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ACUTE ENCEPHALITIS IN CHILDHOOD*

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In this paper I shall deal with the subject of encephalitis in childhood from the point of view of a neuropathologist interested for more than twenty years in the correlation between clinical presentation and histopathological findings.

Physicians who encounter these cases almost daily must feel with me the vital necessity for their earlier recognition, this being the essential condition for their defeat. From this point of view my experience of clinicopathological correlations affords me little satisfaction. As an exercise in modesty and self-criticism I cannot imagine anything more effective than the preparation of this paper.

If we are honest with ourselves and try to discover what it is we really have in mind when we use the term encephalitis, we would probably say "a morbid process, inflammatory in nature, occurring within the brain," and if we wish to be more precise we would add that the process develops in the presence of a living infective agent, acting locally.

Here we already have our first difficulty. In the course of an infectious disease—for example, German measles or bronchopneumonia—it is a commonplace to observe the features indicating disordered cerebral function—drowsiness, confusion, oneirism, and so on. These features precede the symptoms characteristic of the disease itself, being associated with the invasive stage and making their appearance with the commencement of fever. In these circumstances, even though we are witnessing cerebral manifestations in response to a general infection, it would be unrealistic to envisage a cerebral inflammation, and we do not in fact believe that the infective agent has penetrated the blood–brain barrier.

There can be no doubt that certain functional changes in the cerebral circulation, especially on the venous side, interfere with the distribution of substances essential to the metabolism of the brain, especially oxygen, and that these same disorders of circulation also impede the elimination of products of metabolic activity, so that a combination of anoxia and intoxication is produced.

We assume that these diffuse disorders are easily and commonly reversible, at least in individuals whose brain has not been damaged by a previous affection.

The physician must be on his guard if this state of intoxication is accompanied by constitutional disturbances of greater severity than is characteristic of the disease, or if focal cerebral or irritative meningeal signs make their appearance, or, again, if the preliminary pyrexial attack is followed by a recrudescence of fever with return of general cerebral disorders of equal or even greater severity. These are the warning signs of an incipient meningo-encephalitis or meningitis.

I shall deal with both these two conditions simultaneously, since, for the pathologist, and perhaps also for the clinician, no encephalitis can be conceived without accompanying involvement of the meninges.

Diagnosis and Significance of Meningo-encephalitis

Repeated vomiting, photophobia, and stiffness of the neck will be present. The optic fundi will show a slight venous engorgement. The cerebrospinal fluid will be clear and normal as regards both cells and protein. There will, however, be an increase in pressure. Clinical examination will show neither a typical nor an atypical pneumonia. The liver will not be enlarged nor will there be a generalized enlargement of lymph nodes. Examination of blood vessels will show no abnormality. We shall be satisfied that we are dealing with an acute serous meningitis, but will be immediately faced with the need to determine its cause.

Leptospirosis cannot be excluded merely because of the absence of jaundice or hepatic enlargement. Leptospires may be isolated from an apparently normal cerebrospinal fluid. To-day it is recognized that leptospirosis is more widespread than had been thought and that a pure meningeal oedema—that is, without change in cell count or albumin content of the cerebrospinal fluid, but with a rise of intracranial pressure, though still moderate in degree—may be the only sign of the penetration of the infective agent into the meningeal spaces. This phase, which we may call "normergic," is no doubt only transient, but it is at this stage that we must act if we are to recover the organism.

Faced with a meningeal reaction without evidence of visceral disease, one must consider also a virus meningo-encephalitis.

It is well known how numerous these viruses are to-day. If we include the rickettsiae, there are more than 60 that are pathogenic for man. Their spread, geographically speaking, is evidence of our inability either to prevent or to treat them. Clinical examination by itself is of little avail in their identification. It is impossible by clinical examination alone to separate an influenza A from an influenza B or a psittacosis from Q fever or primary atypical pneumonia. On the other hand, each of these diseases may be identified by

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a specialized laboratory. This identification, however, is dependent upon one condition: that the physician who suspects involvement of the nervous system should notify such a laboratory of his suspicion and send at the earliest opportunity specimens of blood, faeces, nasopharyngeal mucus, sputum, saliva, or cerebrospinal fluid.

It is not sufficient to seek the virus in the blood. There are diseases in which it is not present in the blood or is extremely difficult to demonstrate. It is now generally recognized that one of the problems of medicine of the future will be the organization of numerous virological laboratories equipped to achieve this early diagnosis. However, we are not here directly concerned with this.

The physician's responsibility is to know in what circumstances he should suspect a viral infection. We must admit straightaway that he will have only presumptive clues to go on; but these, nevertheless, are worth retaining, for indeed there is nothing better. Of course, in addition to the classical virus infections (influenza, smallpox, poliomyelitis, epidemic encephalitis, and the acute specific fevers) we now have new entities such as psittacosis, epidemic hepatitis, lymphocytic choriomeningitis, and infective mononucleosis.

For the physician, an infectious disease comprises in general one or several initial rigors, a cycle during which the temperature rises and then falls by lysis, a crisis or turning-point, a leucocytosis in the blood with shift to the left and leucocytes with toxic granulations, and a tendency to suppurative lesions.

These signs are often absent in viral diseases. Indeed, should they be present one must suspect an intercurrent infection.

Positive Signs of Viral Disease

As for the positive signs of viral disease, these comprise a biphasic development of fever, bradycardia, a relative leucopenia with lymphocytosis, prominent initial constitutional disorders followed by symptoms of disordered function of the organs—for example, the brain, lungs, liver, intestines, etc.—a tendency to show epidemicity, and, finally, with certain exceptions, resistance to sulphonamides and antibiotics. We may, in passing, point out that the biphasic character of the fever has a certain general biological significance. Its first period (of four or five days) usually corresponds to the phase of viraemia, the second period to the phase of localization of the infection to a particular system of the body (nervous system, viscera, skin, etc.). The first phase is made manifest by non-specific constitutional disorders which vary little in form; this makes them so much more difficult to recognize. It is therefore not surprising that certain infections can be diagnosed only when they have attacked a particular body system; that is, when the first signs of localization within the system become manifest.

I need hardly mention that each of the viral infections of the nervous system has its sites of predilection: posterior root ganglion, anterior horns, substantia nigra, and so on.

It is the association of the focal signs with a history of contact with particular animals (the horse in equine encephalomyelitis, mice in lymphocytic choriomeningitis, pigs in leptospirosis, sheep in louping ill, and so on) which suggest the aetiological diagnosis to the clinician.

However, things are not always straightforward. As already pointed out, the involvement of a particular body system in the second febrile phase is an expression of localization of the viraemia, and the foci within the affected system are an expression of the degree of selectivity shown by the virus. One cannot be sure, however, that this second febrile phase is not due to the superimposition of a second and different viral infection on the first, this second infection deciding the site of the foci. Indeed, it seems probable that this is a fairly common situation. We have only to think of buccal herpes (a cutaneous localization) superimposed upon one of a wide variety of meningitides; the types of tonsillitis and pharyngitis which accompany primary atypical pneumonia; the types of enteritis without demonstrable bacterial causes which accompany smallpox; or poliomyelitis and epidemic hepatitis.

One last example seems particularly important to me. Recently, diarrhoea affecting infants and young children has been recognized from which an agent has been isolated that can be inoculated upon the cornea of a rabbit in the same way as can herpes virus. Until recently this virus has been confused with that of herpes because it also causes a contagious stomatitis. The same virus has been isolated from the genito-urinary tract of adults. Just as in the case of herpes, one may conceive in the case of this new virus that the newborn infant becomes infected as it traverses the birth passages of the mother. However, one cannot exclude the possibility of a member of the nursing staff acting as a healthy carrier, which would explain the occurrence of epidemics in crèches and children's homes.

These features that I have just outlined are not—and this should be emphasized—specific for viral infections. They are equally characteristic of the infections that one used to call pseudoviral, the best-known varieties of which are the leptospiral and rickettsial infections.

These positive and negative features have, nevertheless, a real diagnostic value.

Allergic Reactions

The second febrile phase comprises, apart from the signs of involvement of particular organs or body systems which I have just mentioned, a reaction reflected in the composition of the cerebrospinal fluid—that is, an increase in cells or protein—while specific agglutinins appear in the blood. These changes in the cerebrospinal fluid are a manifestation of the interaction of viral antigen and antibodies—that is, they represent an allergic defensive reaction. In the late stages of the infection, in proportion as sensitization develops, a phase sets in characterized by cyto-albuminological dissociation associated with an abnormal colloidal reaction. This last phase is an indication that the antigenic and pathogenic agent has not been eliminated.

So long as an infection of the nervous system is unaccompanied by focal signs, and the cerebrospinal fluid remains normal, it is not customary to speak of an encephalitis. This is, of course, a convention rather than an absolute truth. If a child succumbs during this initial phase we speak of a toxic encephalopathy—that is, a diffuse toxic affection of the cerebrospinal axis—because anatomical studies fail to reveal the presence within the cerebral parenchyma of inflammation in the general pathological sense—that is, a process characterized by exudation and cellular proliferation.

In actual fact there are cases that are extremely difficult to analyse, which perhaps it would be wrong to exclude from the domain of true inflammation, so much the more so since the introduction into general pathology of the concept of serous inflammation. One observes from time to time, both in infants and in young children, cerebral disorders with an acute and fatal course, which reproduce exactly in their clinical development and anatomical substrate what is seen in the endogenous and exogenous intoxications.

It is worth while pausing for a few moments over this picture of an acute serous inflammation of the brain, which may or may not be accompanied by an acute involvement of the myocardium or liver. This condition is encountered in young children suffering from an acute gastro-enteritis. The only premonitory signs are repeated vomiting and diarrhoea, with or without colic. At this point a sudden circulatory collapse supervenes, with coldness of the extremities, cold sweating, and anxiety. Death follows within two to five days, sometimes without fever developing. Bacteriological examination is negative and necropsy equally disappointing; the liver is oedematous, its parenchyma slightly dissociated with focal fatty degeneration; the brain is swollen, with engagement of the cerebellar tonsils; the myocardium shows stasis, with slight hyaline swelling of the walls of the vessels; the lungs are the site of a slight oedema; and the kidneys show epithelial desquamation of the tubules. One is forced to conclude that a toxic agent has severely disturbed the permeability of the capillaries, resulting in an infiltration of the interstitial tissues with diapedesis of red cells and plasma, and disturbance of tissue respiration. In the brain the disturbed equilibrium of permeability results in cerebral oedema, such as we are familiar with in uraemia, eclampsia, and epilepsy.

In the cases we have been able to observe there always have been, at the onset, intestinal upsets sometimes accompanied by fever. Intestinal infection by micro-organisms of high toxicity or even viruses may cause an increased permeability of the intestinal mucosa. This breakdown of the filtering mechanism of the intestines allows the passage of colloidal substances (albumin or breakdown products) to which the tissues of the bowel wall may become sensitized. Their further absorption will result in an allergic reaction culminating in an acute serous inflammation.

From a personal point of view, it seems difficult to reject such cases of acute serous inflammation of the brain from the encephalitis group merely on the grounds that the exudation is serous rather than cellular. On the other hand, one can well understand the uneasiness many feel when asked to consider as inflammatory a process which is morphologically identical with that resulting from an exogenous intoxication and perhaps developing, like the latter, without fever.

Bickerstaff and Cloake (1951), in England, have described an encephalitis of the brain stem. In this condition there is a severe affection of the third and other cranial nerves, of the supranuclear oculomotor pathways, disorders of deep sensation, and of the pyramidal tracts. The symptoms develop and then recede over a period of weeks or months. Cure is the rule and sequelae are exceptional. According to the authors, the most remarkable feature of the illness is the contrast between the extreme severity of the patient's condition at its worst and the favourable outcome which is the rule. The only case which was subjected by Woolf to post-mortem examination was that of a boy aged 14 years in whom the only lesions were those of oedema, a few very localized perivascular infiltrations in the frontal region, and periportal round-cell infiltration. The authors regarded the malady as the central equivalent of an infectious viral polyneuritis. The cerebrospinal fluid showed a pleocytosis with cyto-albuminological dissociation suggesting a still active infection rather than an allergic state. The presence of inflammatory hepatic lesions would support this interpretation.

Acute Haemorrhagic Encephalitis

In considering those cases where involvement of the capillary system results in diapedesis of red blood cells, we enter the domain of acute haemorrhagic encephalitis or encephalopathy, in which we shall, no doubt, run into the same difficulties in classification.

These serous or serohaemorrhagic encephalitides in the guise of acute oedema can be observed in the types of gastro-enteritis just discussed. They may also occur in the acute exanthemata, in influenzal states, and in anaphylactic shock. The symptomatology is always the same: nausea, malaise with a tendency to circulatory collapse, profuse sweating, hyperpyrexia, convulsions, coma, and death. The cerebrospinal fluid is clear or blood-stained, or, much more rarely, xanthochromic. The treatment is again that of severe medical shock. Should there be added to such a picture a simple ascending or descending hemiplegia or a hemiplegia with a tendency to bilaterality, it is more likely that we are dealing with another syndrome: that of acute infantile encephalopathy due to venous thrombosis or thrombophlebitis, the anatomical substrate of which is haemorrhagic infarction with oedema. In some cases there is also a meningeal haemorrhage.

This complication can supervene in the course of any cranio-facial infection, in many general infections, especially measles, scarlet fever, typhoid fever, and whooping-cough, but also, without obvious cause, in marasmic infants or young children. In an important work, Woolf (1955) stressed the significance of thrombosis of the superior longitudinal sinus in acute infantile cerebral diplegia. The condition to which he has drawn attention may develop without convulsions and in children who have previously been normal.

It is obvious that the field of phlebitis and marasmic thrombosis will shrink in proportion as we recognize earlier and more accurately these cryptic infections and realize that they are responsible for the thrombosis, and not the anaemia and dehydration which are usually blamed.

While one may hesitate in the case of the acute infectious or fulminant post-infectious encephalitides to dogmatize on the inflammatory or degenerative nature of the cerebral lesions, the situation is different in regard to the thrombophlebitic encephalopathies. There can be no doubt that the thrombosis results from a change in the walls of the veins or a disturbance of the blood, but it is by the intermediary of necrosis that the focal neurological signs are produced, the necrotic component being out of all proportion to the inflammatory component of the lesion. We are therefore dealing with a post-infectious encephalopathy.

Not all so-called idiopathic cerebral venous thromboses occur in the circumstances we have just outlined.

A few cases arise from the venous counterpart of an obliterative endarteritis of Winiwarter–Buerger, a migrating manifestation of thrombosis elsewhere, or a polyarteritis nodosa. All these conditions are, however, rare in childhood.

One should not only take stock of the paralytic features but look for evidence of cranio-facial venous stasis such as oedema of the soft parts or retinal venous thrombosis. This is scarcely the place to elaborate the picture, for these syndromes of cerebral venous thrombosis are classic, at least in Britain, where for the school of neurology they are a matter of everyday experience. It will suffice for me to add that the persistence of gross paralysis or the appearance of a purulent meningitis demands the rejection of the diagnosis of encephalitis, and puts the physician on his guard lest a cerebral abscess develops subsequently, especially if there has not been a prompt administration of antibiotics.

On the other hand, the presence of a cerebral tumour or abscess may be stimulated by otitic hydrocephalus. In this condition a child first presents with an acute otitis or, more often, a recrudescent old otitis, especially on the right side. This may be followed, with or without accompanying headache, by a third-nerve paralysis on the side of the infected ear together with papilloedema. The patient's general condition remains very good or only slightly affected; the cerebrospinal fluid remains normal or its tension may be increased. The ventricles are of normal size or smaller than normal. The picture suggests an excess of cerebrospinal fluid. Whether this results from hypersecretion of the choroid plexuses or defective absorption is still a matter for discussion, but there can be no question of explaining the raised intracranial pressure in terms of mechanical obstruction to the cerebrospinal fluid pathways. In order to avoid any suggestion of an inflammatory origin or dogmatic postulation of the site of the accumulation of fluid, Sir Charles Symonds proposed the name "otitic hydrocephalus." We shall not pause to consider the mechanism by which this disorder is produced, preferring to abide by the name suggested by Sir Charles because it characterizes so well the clinical features even though there are some who find it too narrow in its implications.

Encephalopathy or Encephalitis?

In acute cases the choice of diagnosis between encephalopathy and encephalitis to a considerable extent depends upon the orientation of the neuropathologist. If he is particularly conscious of the diffuse neuronal changes he will regard the case as an encephalitis; if, on the other hand, the vascular stasis and oedema make the deeper impression upon him, he will favour a diagnosis of encephalopathy in the course of a fulminant post-infection encephalitis. One can sense the hesitation of neurologists and neuropathologists to commit themselves in the names commonly employed to describe these conditions—malignant state, acute neurotoxicosis, dysmetabolism of infants, diffuse toxic encephalitis or encephalopathy, and so on. This uneasiness results, of course, from the minimal lesions which must form the basis for our diagnosis.

It must be stressed that the encephalitides are in reality far less common than is suggested by the number of cases sent to us with this diagnosis; in fact, they are much less common than the encephalopathies. It is therefore not without interest to recall briefly which encephalitides are most often encountered in Belgium.

Since acute encephalitis is most frequently an episode in the course of a more generalized disease one bases one's diagnosis on the symptomatology of the generalized disease—for example, mumps, primary atypical pneumonia, and glandular fever. Theoretically, at least, one may also encounter acute encephalitides complicating psittacosis or shingles. Acute herpetic encephalitis in the infant has, on the other hand, a very characteristic picture, but should be diagnosed only after careful consideration.

The acute post-infectious encephalitides can occur in exceptional cases in the course of an unobtrusive basal pulmonary infection or may even precede the clinical signs of the latter. The diagnosis is extremely difficult, especially when the encephalitis is fulminant. The child passes from normality to coma with hyperthermia, with or without convulsions and with or without cardio-respiratory collapse. If it develops a hemiplegia the chances of there being an encephalopathy are obviously greater. Such fulminant post-infectious encephalitides preceding the clinical manifestations of basal infection are, however, exceptional. Faced with a case of "comatose encephalitis" one will be right nine times out of ten in diagnosing an encephalopathy. No doubt one does see in whooping-cough, measles, and scarlet fever exceptional cases with a fulminant course, where the picture is that of a diffuse haemorrhagic encephalitis with blood-stained cerebrospinal fluid. These cases cannot be separated from the encephalopathies described in the course of these diseases, when they appear in the invasive phase, at the beginning of the phase of focal symptoms, or during a flare-up with return of fever.

Cerebral Herpes

I must now deal briefly with two types of encephalitis that may be encountered. The first is herpetic encephalitis. Here we may distinguish two forms. In the first, an infant, especially a premature infant, after an alarming phase of rigidity becomes irritable or stuporous, its temperature rises, there is cyanosis with extreme dyspnoea, and the conjunctivae appear jaundiced or subicteric. The infant has diarrhoea, vomiting, and, most characteristically, epistaxis, melaena, haematomas at injection sites, and cutaneous herpetic lesions becoming unrecognizable because of their tendency to ulceration, necrosis, confluence, and haemorrhage. The liver and spleen are enlarged. Myoclonus and convulsions ensue, and death occurs, ushered in by severe shock and subnormal temperature.

What is seen is in essence a fulminant polyvisceral disease with a predilection for the liver and brain. At necropsy, the liver, suprarenal cortex, lungs, spleen, and bone marrow are peppered with necroses containing acidophil inclusions. The focal cerebral lesions are those of an acute post-infectious disseminated encephalitis and are not the result of direct damage to the brain by the herpes virus.

In the other form of cerebral herpes the onset is cerebral. Usually the patient is an infant several weeks old. The onset is abrupt, with delirium, convulsive seizures, and opisthotonos; sometimes there are paralyses and spontaneous movements of the extrapyramidal type, together with cutaneous or mucosal

herpes, with death following in eight to ten days. The cerebrospinal fluid is often clear, but may be haemorrhagic, with an increasing number of white cells up to 1,000 per c.mm. accompanied by an increase in the protein. At necropsy there is severe necrotic encephalitis, usually with an asymmetrical bilateral temporal-hippocampal distribution, causing the affected brain to have a creamy consistency. This is the picture of acute herpetic encephalitis with direct damage to the brain by the herpes virus.

Acute Necrotizing Encephalitis

Closely related to herpes encephalitis is the condition termed by Greenfield (1950) "acute polioclastic encephalitis," and by van Bogaert *et al.* (1955) as acute necrotizing encephalitis. Exceptionally it occurs in childhood. The onset is usually hepato-intestinal, pharyngeal, pulmonary, or simply general and indeterminate. Severe disturbances of consciousness rapidly supervene—for example, mental confusion with agitation, olfactory or visual hallucinations, and Jacksonian or generalized convulsions. There may be a hemiplegia with signs of cranial-nerve involvement. The cerebrospinal fluid shows a lymphocytic pleocytosis with a normal or moderately increased protein content. Death usually follows within 5 to 15 days, but may be delayed beyond this time. At necropsy there is a violent inflammatory necrosis of the superficial layers of the brain, with large neighbouring areas of paling in the hippocampus, temporal lobe, insula, and callosal-marginal regions. Inoculations are negative, but inclusions of type A are seen as in herpes. The autonomy of this condition is doubtful and further studies are indicated. In this condition, also, the differential diagnosis is from thrombophlebitis of the posterior cerebral veins or temporal lobe abscess.

Leucoencephalitis

Between the cases of acute haemorrhagic encephalitis occurring at the onset or first phase of an infectious disease and the later neurological complications mentioned below is a small group of cases which will show either a serohaemorrhagic pattern or, if they survive longer, a pattern of perivenous glial encephalitis. I mention these cases because they have been first described in Australia by a graduate of Birmingham University—Hurst (1941)—under the title of "acute haemorrhagic leucoencephalitis." These cases can hardly be diagnosed during life, but can be identified with certainty by port-mortem examination.

The acute encephalitides which I mentioned earlier are contemporaneous with the first or second febrile phase of viral disease—that is, with the viraemic or normergic phase of the illness. Cerebral complications may, however, supervene at a later or much later stage.

The physician should think of the allergic type of post-infectious encephalitis whenever an exanthematic fever, whooping-cough, influenza A or B, or even a banal respiratory infection is followed after a certain delay, with or without return of fever, by the slow, insidious, and progressive development of neurological symptoms and signs. In other cases there is a fresh spike of temperature and rapid development of coma. In the less severe cases the clinical picture is made up of a mixture of successive cerebellar, choreiform, and pyramidal symptoms together with cranial nerve signs. Because of the predilection of the lesions for the white matter, these cases are often called post-infectious leucoencephalitides. They are nowadays well recognized and in most cases the prognosis is very favourable.

When no primary disease is discovered, one refers to a primary leucoencephalitis. Those favouring this term believe that the leucoencephalitides result from the activities of a virus which in most cases is activated by vaccination or by an insidious primary disease. Others believe that the primary disease has passed unnoticed and is only made manifest by the late—"allergic"—neurological complications.

At this stage the cerebrospinal fluid usually shows the albuminocytological dissociation and abnormal colloidal reactions that I mentioned earlier.

Late Encephalitides

The late post-infectious or allergic encephalitides can last for weeks or even months. Their progress often remains good in spite of the severity of the clinical picture, which may go as far as decortication or decerebration, reducing the child for weeks to a purely vegetative existence and necessitating the most skilled nursing. The clinical picture of the late encephalitides is well known. Many studies have been published on those that follow chicken-pox, measles, and vaccination. Each of these primary diseases has a tendency to produce cerebral complications with a particular profile. This profile is, no doubt, not exclusive; it is merely that one finds a neurological picture of one particular profile more commonly after one primary disease than after the others. The late encephalitides remain an admirable field for those who study encephalitic phenomena in their general biological context, together with other articular, serous, or muscular manifestations of these infections. They may even provide a means of access to the as yet unknown mechanisms which underlie the genesis of the demyelinating diseases.

It is highly probable that a very small part of the allergic encephalitides, occurring without obvious primary disease, represents the initial stages of disseminated sclerosis. This eventuality, so ominous for the subject concerned, is certainly exceptional, and if an encephalitis should leave a child with a certain number of sequelae (epilepsy, disturbance of character, etc.) the inference should rather be one of multifocal healed lesions due to the encephalitis.

Treatment

I have attempted to deal only with the acute encephalitides of childhood, because it is these which pose to the physician the most delicate diagnostic and therapeutic problems. If their diagnosis brings home to us our ignorance, how much more so does the question of treatment.

The physician must, of course, deal with the primary disease of which the encephalitis is only a localized feature. The cerebral complication will, however, also engage his attention, as it affects both immediate and remote prognosis.

The affection of the nervous centres may result in disturbances of ionic balance in the blood, exhaustion of the cerebral and the peripheral autonomic control which participates in the general defence mechanisms of

the individual, changes in coagulation of the blood, and disturbances of the blood–brain barrier. This constellation of factors has its effect upon the symptomatology. Coma or convulsions may develop, or hypothermia or hyperthermia require our therapeutic intervention.

Within the group of cases probably, or possibly, due to cerebral thrombosis or thrombophlebitis, otitic hydrocephalus has a tendency towards spontaneous cure except in cachectic infants or children. Indeed, one may say that it is the only variety of cerebral thrombosis or thrombophlebitis in childhood in which the prognosis is not very gloomy. Palliative measures (repeated lumbar punctures, limitation of fluid intake, and anticonvulsive medication) are in other thromboses of little avail. The advisability of anticoagulant therapy is still under discussion. It certainly carries with it a serious danger if the cerebrospinal fluid is blood-stained. Our own view, however, is that, having regard to the severity of the illness before us, especially if the cerebral signs are progressive and the seizures show a tendency to become generalized, it is better to make use of the chance of success which the anticoagulant remedies offer. We would say that these remedies are particularly indicated where (though this is rare in childhood) the cerebral event is accompanied by thrombosis of the vessels of the limbs.

In the fulminant encephalopathies without hemiplegic signs and where there is no suggestion of thrombosis, the essential aim is the restoration of the ionic equilibrium of the blood. One must attempt to block the autonomic system by chemical insulation and should not, therefore, hesitate in the presence of convulsions to give barbiturates by transfusion.

Let us suppose a diagnosis of encephalitis, and probably a virus encephalitis, suggests itself; most of the viral encephalitides are, with rare exceptions, insensitive to both the antibiotics and the sulphonamides. We shall therefore reserve these two groups of substances for the treatment of the accompanying secondary infections. On the other hand, we will, of course, employ salicylates and iodine in high dosage as we did during the European encephalitis epidemics in 1920–5. Recently a place has been given to cortisone and corticotrophin in the treatment of these acute forms as well as the late forms of post-infectious encephalitis. In the acute forms we have not had the impression that these substances are of undoubted value. In regard to the late forms it is difficult to evaluate a therapy in a condition where the natural outcome is in any case so favourable.

In the presence of coma, and especially in the presence of those prolonged states of disturbed consciousness which are seen in late post-measles encephalitis, the treatment will be that usually given in the state of common shock.

I have mentioned the serous encephalitides; their treatment will also be that of states of severe shock.

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THE ELECTROENCEPHALOGRAM IN MYXOEDEMA COMA

CLINICAL AND ELECTROENCEPHALOGRAPHIC STUDY OF THREE CASES*

BY

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Myxoedema as a cause of death was first described by Hadden in 1879, when a patient under the care of Ord (1878) died in coma. That myxoedema might be other than an easily remediable condition, however, was largely ignored until recent reports made it clear that myxoedema coma was not in fact a rarity, and that it was almost invariably fatal. During the past four years at least 20 cases have been reported in this country alone—all these patients died except one in the series reported by Malden (1955). Summers (1953) reported five cases in which the patients died in hypothermic coma, the initial temperatures varying from 23.9 to 35° C. Treatment by immersion in a warm bath, thyroxine, and cortisone had no effect. Dyson and Wood's (1956) patient died after 100 μg. of triiodothyronine had been given intravenously. Malden (1955) reported three cases of hypothermic coma; two patients died but one recovered after treatment with electric blankets and intravenous corticotrophin and thyroxine. He noted that hypothermia was present in all three cases, the blood sugar was normal, and there was absence of shivering (due, he supposed, to failure of the thermo-regulatory centre).

Reports of recovery have been remarkably few. Apart from the case of Malden (1955) only two other survivals have been described; one a very early case which recovered spontaneously in 24 hours (Brotmacher and Coghill, 1953), the other a condition of deep coma in a woman of 83 who recovered with thyroid extract, but in whom the temperature was not noted (Martin and Whittle, 1953). That it is an extremely dangerous condition, however, is evident, and Summers (1953) thought that the changes produced by extremely low body temperatures are apparently irreversible or that the body reaches a state in which it can no longer respond to thyroxine.

Coma in myxoedema patients presents a clinical picture similar in many respects to coma in hypopituitarism (Sheehan and Summers, 1952). Caughey and Garrod (1954), in discussing factors which could precipitate coma in hypopituitarism, mentioned infection, hypoglycaemia, hypersensitivity to drugs and anaesthesia, sodium depletion, water retention, cerebral anoxia, and hypothermia as possible factors. It is possible that some of these factors may also operate in the production of myxoedema coma and that adrenocortical failure or even some degree of pituitary failure (Hubble, 1955) may be concerned.

It is interesting to note the effect of artificially induced hypothermia in man and animals. Dundee, Scott, and Mesham (1953) found that cardiac arrest occurred in three dogs at temperatures of 23° C., 25° C., and 26.5° C. Swan *et al.* (1953), however, described temperatures ranging from 21.5 to 26° C. in 15 patients

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undergoing cardiac operations with only one fatality. It therefore seems unlikely that hypothermia is the sole factor in preventing recovery from myxoedema coma, though it is doubtless an important one. One would expect that cerebral activity would be markedly affected in these cases (as of course the state of consciousness indicates). Scott (1955) has described the E.E.G. changes in hypothermia in man and found that cerebral electrical activity was much reduced, though it did not entirely disappear.

I have been able to find only one report of the E.E.G. changes in myxoedema coma. Biemond (1955) described the case of a woman of 66 who was stuporous when an E.E.G. was taken. She later died from bronchopneumonia and was found to have cirrhosis of the liver and cerebral changes of Wilson's disease as well as thyroid aplasia. There was no mention of hypothermia. The E.E.G. revealed "a dominant theta rhythm of 6–7 cycles per second at 30–40 microvolts; there was also some generalized 2–3 per sec. delta activity." Serial E.E.G.s have been taken in a case of hypopituitary coma by Salmon (1956). The coma was associated with hypothermia (87° F.; 30.6° C.), hypoglycaemia (blood sugar 35 mg./100 ml.), and sodium depletion (serum Na 276 mg./100 ml.). Treatment restored the patient (and her E.E.G.) to normal. He remarks that the form of the initial tracing (high-amplitude delta activity) was probably due to the hypoglycaemia.

I have been able to obtain E.E.G.s of two patients in myxoedema coma and a third patient during recovery from the same condition. They illustrate three phases of the same process and the accompanying changes in cerebral electrical activity.

Case 1

A married woman aged 62 was admitted in coma to the Royal Southern Hospital, Liverpool, under the care of Dr. R. W. Brookfield, on January 14, 1958. Although a known case of myxoedema, she had taken no thyroid for two years. On the night of January 13 (a very cold night) she went to bed, and next morning was found on the floor in her nightdress and could not be roused.

On admission her rectal temperature was 24.5° C. (76° F.). She was deeply comatose and unresponsive to any stimuli. An obese woman, she presented a grossly swollen, typically myxoedematous facies with coarse, dry, ice-cold skin. Her axillary hair was sparse, but her pubic hair was normal. Her respirations were slow and grunting, her pulse was impalpable, and her heart rate was 20 a minute. Her serum cholesterol was 440 mg., sodium 285 mg., potassium 16 mg., and sugar 80 mg./100 ml. Her E.E.G. on admission (Fig. 1) showed in addition to artifact (from head movement and snoring) an almost flat trace with a few random 4–5 c./sec. waves (10 μV). She was catheterized on admission, the bladder containing 120 ml. of urine. As it was known she had passed urine about 12 hours previously it was possible to make an estimate of 17-ketosteroid excretion during the preceding 24 hours (1 mg.). Treatment was begun as follows: (1) She was covered with blankets and a heat cradle placed outside; (2) 100 μg. of L-triiodothyronine in 500 ml. of 5% glucose-saline was given by intragastric drip; and (3) 100 mg. of hemisuccinate hydrocortisone was given intravenously.

During the next 24 hours her general condition did not change, but her rectal temperature rose from 24.5 to 27° C. However, she died 24 hours after admission. Further blood was taken about 10 minutes before death, and the estimations were as follows: serum sodium 320 mg., potassium 15 mg., and sugar 135 mg./100 ml. She was catheterized after death—there had been no secretion of urine in the previous 24 hours. A post-mortem examination was not permitted.

Comment.—This is the type of case which led Le Marquand, Hausmann, and Hemsted (1955) to remark: "We were impressed . . . with our helplessness to deal with the final phase." It is difficult to see how with our present therapeutic armamentarium this patient could have been saved, especially as in recent cases intravenous triiodothyronine has brought no improvement (Dyson and Wood, 1956) and may indeed be dangerous in producing a too rapid acceleration of metabolism. The E.E.G. tracing in this case indicates that cerebral electrical activity was reduced to a minimum although it does not follow that any permanent brain damage would have ensued had recovery taken place.

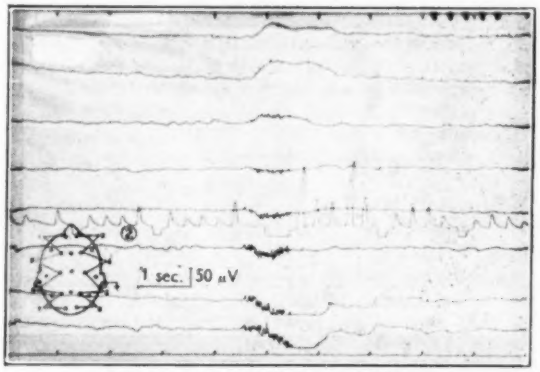

FIG. 1.—Case 1. E.E.G. on admission.

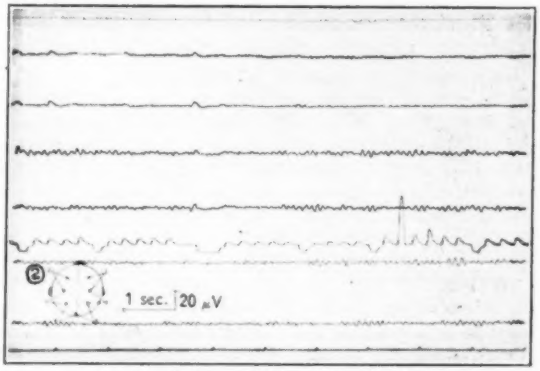

FIG. 2.—Case 2. E.E.G. on June 14, 1955.

Case 2

This case illustrates the condition of myxoedema coma at an earlier stage, when recovery was possible with the use of thyroid extract.

A married woman had a subtotal thyroidectomy for non-toxic goitre in 1953 at the age of 45. Shortly after this she was judged to be hypothyroid and given thyroid, 1½ gr. (0.1 g.) daily, with benefit. In June, 1955, her skin was somewhat dry and she was occasionally forgetful, but was otherwise quite well. Her E.E.G. at this time (Fig. 2) showed a 9 c./sec. alpha rhythm with an amplitude of 10 μV.

On September 3, 1957, she started to vomit, and two days later was admitted to the Royal Southern Hospital. She was found to be drowsy and uncooperative; she answered questions with difficulty and was dehydrated. The dehydration was corrected, the vomiting ceased and her serum electrolytes and N.P.N. were normal. However, she

became gradually weaker, more apathetic and quiet, drowsy, and difficult to rouse. By September 12 she was stuporous. She slept most of the time and would respond, by moving, to shouting and to painful stimuli, but would utter no more than a few drowsy words. She felt very cold: her temperature was recorded as 96° F. (35.6° C.), but was probably lower as a clinical thermometer was used. Her N.P.N. was 20 mg./100 ml., serum cholesterol 140 mg./100 ml., and 17-ketosteroids 2.8 mg. a day. At this stage it was discovered that she had not received any thyroid for six months. A diagnosis was made of myxoedema coma, and thyroid extract was given (via a Ryle tube). An E.E.G. (Fig. 3) obtained just before thyroid was started showed a

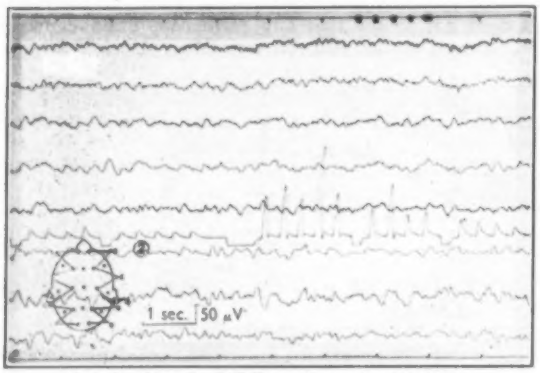

FIG. 3.—Case 2. E.E.G. on September 12, 1957.

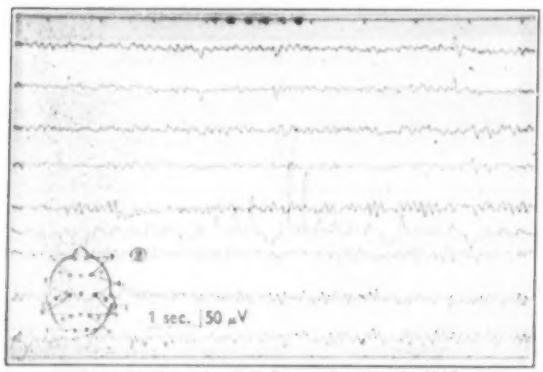

FIG. 4.—Case 2. E.E.G. on October 2, 1957.

mixture of generalized 3 c./sec. delta activity and 5–6 c./sec. theta activity with an amplitude up to 50 μV. A very small amount of 8–9 c./sec. alpha activity was detected in the parieto-occipital leads and a little rapid activity anteriorly.

She remained drowsy and apathetic (with lapses into coma when she could not be roused) for several days, although no further vomiting occurred. However, on September 20 she appeared more alert, though still sleepy and lethargic. Progress continued slowly, and on September 25, when a further E.E.G. was obtained, she was sleeping less and could recognize objects and talk lucidly at times, though her attention wandered. The E.E.G. showed some improvement—a fairly regular 7–8 c./sec. occipito-parietal alpha rhythm with much 4–6 c./sec. theta and a little low-amplitude delta activity in the temporal regions.

On October 2 she looked much less hypothyroid, was more alert, and could hold a cup. Her speech was slow and her memory poor. The E.E.G. (Fig. 4) showed a somewhat irregular 8 c./sec. alpha rhythm with scattered 6–7 c./sec. waves in all leads. On October 10 she was starting to walk and could feed herself. She knew the date and could tell the time, but could not attempt the 100–7 test. Her skin was still dry without axillary sweating, otherwise her appearance was normal. Her E.E.G. showed a mixture of 8 and 9 c./sec. alpha activity posteriorly with a regular 7–8 c./sec. rhythm anteriorly. She was discharged on October 12, taking thyroid, 3 gr. (0.2 g.) daily. On November 26 she was seen again and appeared euthyroid, her only deficit being a rather poor memory for recent events, and a poor performance at mental arithmetic (failing the 100–7 test at 79). The E.E.G. showed an 8–9 c./sec. alpha rhythm, with no slow activity.

Comment.—In this case the episode of coma (less severe than in Case 1) appears definitely to have been associated with her hypothyroid state, although it was probably precipitated by vomiting and dehydration. At the time when she was comatose there was no clinical or biochemical evidence of dehydration, nor, as she was receiving dextrose by the intragastric route, could hypoglycaemia have played a part. Focal neurological signs were absent. Moreover, the gradual response to thyroid extract alone with concomitant gradual E.E.G. improvement suggests that this was indeed an episode of myxoedema coma. Treatment, of course, was begun at a much earlier stage than in Case 1 and when a response was possible to an agent as slow in action as thyroid extract. It seems reasonable to suggest that had the condition been allowed to progress further a more rapid agent such as thyroxine or triiodothyronine would have been required, and if treatment had been further delayed no response to treatment might be forthcoming. One may postulate a dynamic concept of a condition which in its earliest stage will respond to small doses of thyroid extract and in its latest stage may be irreversible because of damage to vital centres, including the brain.

An intermediate stage in which more rapid and energetic treatment may yet produce a response is exemplified by Case 3. (Also reported by Surtees and Ginsburg, 1958.)

Case 3

A married woman aged 70 had complained for one year of increasing coldness, gain in weight, deafness, and a puffy face. For one week she had been sleeping more than usual. On the morning of January 22, 1957, she had been found in bed and could not be roused. On admission to Walton Hospital under the care of Dr. V. K. Summers, she was stuporous and very restless. She looked myxoedematous with a yellowish puffy face and dry scaly skin. Her rectal temperature was 87° F. (30.6° C.). The axillae were dry and hairless, and the pubic hair was scanty. Neurological signs were absent. The pulse was regular at 52 a minute, the heart sounds were faint, and the blood pressure was 180/100. Her blood sugar was 122 mg., serum potassium 19 mg., serum cholesterol 645 mg., serum sodium 290 mg./100 ml., and haemoglobin 82%. The E.C.G. was negative T123.

She was treated initially by means of a heat cradle, and 100 μg. of L-triiodothyronine was given by Ryle's tube. There was little change in the first 24 hours, but by 48 hours she was less drowsy, was speaking a few words, and her rectal temperature was 99° F. (37.2° C.). Treatment was continued with triiodothyronine, 40 μg. a day. By January 25 she was speaking and was much more active. On February 2 the B.M.R. was −25%. On February 6 she was speaking rationally, and seemed normal mentally; the pulse and temperature were normal. An E.E.G. (Fig. 5) showed a dominant 8 c./sec. alpha rhythm with a good deal of scattered 7 c./sec. activity. The highest amplitude was in the temporal leads (up to 14 μV) with very low frontal voltage. Triiodothyronine was stopped on February 13 as she felt weak and giddy, started to vomit, and developed tachycardia. Cortisone, 25 mg. a day, was given. On February 18 her condition had improved again: a further E.E.G. (Fig. 6) showed an 8 c./sec. alpha rhythm

in the parieto-occipital regions (15 μV) with an increase in the amount of 7 c./sec. activity and a dominant 7 c./sec. frontal rhythm (suggesting that some deterioration had taken place).

Unfortunately the patient died suddenly on February 18. Necropsy revealed that death was due to a thrombosis of the right coronary artery. The thyroid was small, consisting almost entirely of fibrous tissue. The pituitary and adrenals were normal.

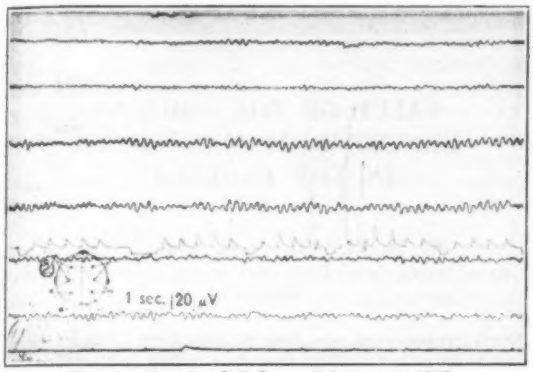

FIG. 5.—Case 3. E.E.G. on February 6, 1957.

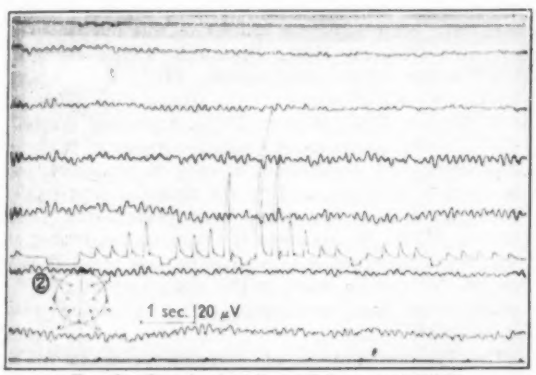

FIG. 6.—Case 3. E.E.G. on February 18, 1957.

Discussion

The electrical activity of the brain is correlated closely with its metabolism. The E.E.G. records differences in potential through the scalp and thereby reflects the behaviour of the brain in its internal environment. Changes in metabolic factors such as oxygen tension or availability of glucose are quickly reflected in the E.E.G. (Davis, Davis, and Thompson, 1938). Shifts in electrolyte balance, *p*H, and particularly CO_2 tension significantly influence the brain waves (Gibbs, Williams, and Gibbs, 1940). This prompt response to alterations in the internal environment of the brain provides a convenient means whereby the physiological effects of disease elsewhere may be detected and correlated with clinical observation.

Neuropsychiatric disturbances occur commonly in endocrine disorders, and abnormalities in the E.E.G. have been described in such conditions as hypopituitarism, Addison's disease, Cushing's syndrome, hyperinsulinism, myxoedema, and thyrotoxocosis. The biochemical disorder differs in these conditions, although ultimately the cerebral disturbances which may occur relate to altered respiratory exchanges in the brain cells. The E.E.G. itself is an expression of the metabolic activity of the brain cells, and its normal features depend on numerous humoral and tissue factors whose stability is regulated, *inter alia*, by the endocrine system. It is logical to suppose, *a priori*, that cerebral bioelectrical activity undergoes important modifications in endocrine disturbances, and this is in fact what occurs.

Three cases of myxoedema coma have been presented. In the first and most severe case, which was associated with an extreme degree of hypothermia (24.5° C.), very little cerebral activity was demonstrable in the E.E.G. record. In Case 2 when coma was light the record showed generalized theta and delta activity of normal or somewhat reduced amplitude. In Case 3 the E.E.G. taken during recovery from coma resembled the records seen in untreated myxoedema of moderate severity in the waking state (Nieman, 1958). Numerous studies have implied that E.E.G. changes parallel changes in cerebral metabolism, and that in delirium and coma from widely differing causes the E.E.G. can be correlated with the clinical evaluation of the level of awareness (Engel and Romano, 1944). In general the E.E.G. in mild delirium shows a shift to frequencies below the normal alpha range; with more marked delirium there is greater slowing of frequencies accompanied by the appearance of intermittent low-voltage fast activity. In a severe derangement of cerebral metabolism the E.E.G. consists largely of irregular moderate to high-voltage 1–8 c./sec. slow waves. Engel and Romano (1944) think it is possible to correlate the E.E.G. picture and the level of awareness with considerable precision. It appears, however, from these cases that, whereas in other forms of delirium and coma the E.E.G. waves increase in voltage whilst decreasing in frequency, in myxoedema both frequency and amplitude decrease together.

There is evidence that the lowering of voltage is due, in part at least, to the hypothermia which may accompany the reduction of cerebral metabolism in myxoedema coma. The extent to which the E.E.G. of a patient in severe hypothermic coma with virtually no cerebral electrical activity demonstrable can recover is, however, uncertain. Whether the E.E.G. will return to normal and whether there will be any residual cerebral symptoms are problems which must remain until more satisfactory treatment can be employed to resuscitate such patients. Some residual mental impairment is present in Case 2—namely, poor memory for recent events and inability to calculate—and this may be the result of cerebral damage during myxoedema coma.

It is notable that hypoglycaemia, which may play a part in the production of hypopituitary coma (Caughey and Garrod, 1954), was not present in any of the above cases, nor does the E.E.G. resemble the tracing seen in hypoglycaemia (Davis *et al.*, 1938); and sodium depletion does not seem to have been responsible. Adrenocortical function, however, as implied by the 17-ketosteroid estimation, was reduced in all three cases, and in the most severe case was only 1 mg. in 24 hours. This does not necessarily imply that hypofunction of the adrenal cortex is responsible for the production of coma in myxoedema. It has been known for some time that adrenal cortex function might be sometimes, though not invariably, depressed in myxoedema. Friedgood (1942) demonstrated low excretion of 17-ketosteroids in 9 out of 10 patients with spontaneous and post-thyroidectomy myxoedema. Therapy did not raise the values.

Hill, Reiss, Forsham, and Thorn (1950) found that 9 out of 11 patients with primary hypothyroidism given a single 25-mg. injection of corticotrophin had an inadequate adrenal response, and Hubble (1955) found a defective water-load response in myxoedema. In a personal series of 18 patients in whom the 17-ketosteroid excretion was estimated the highest figure was 5.7 mg. a day and the lowest 0.95 mg. a day. In all but two patients the figure was below 5 mg. a day. Boulet and Mirouze (1955) believe that if adrenal function is investigated in myxoedema then hypocorticalism will be found almost as constantly as hypothyroidism: they emphasize, however, that thyroid hormone is the only treatment indicated. It is difficult, therefore, to assess the role of the adrenal cortex in the mechanism of myxoedema coma. It is unlikely to be a major factor, as clinical evidence of adrenal insufficiency is not found in myxoedema coma, and Summers (1956) found that cortisone was of no value in the treatment of myxoedema though it might produce some mental alertness. Moreover, the E.E.G. in myxoedema and in myxoedema coma does not resemble the records seen in Addison's disease (Hoffman, Lewis, and Thorn, 1942).

It is probable that hypothermia, which is a constant feature of myxoedema coma, and deficiency of thyroid hormone itself, are the most important factors, though precipitating factors may include environmental cold (note the seasonal variation), trauma (Macdonald, 1958), and dehydration (Case 2 of present series). Macdonald (1958) suggests that during periods of stress the requirement of thyroid may increase like that of the adrenal corticosteroids. In advanced myxoedema coma the tissues may become unresponsive to thyroid hormone and the condition be irreversible. Extreme reduction or absence of cerebral electrical activity may indicate this state of affairs and a poor prognosis.

Summary

The clinical features and E.E.G. traces in three cases of myxoedema coma are described. It is suggested that thyroid hormone deficiency and hypothermia are the most important factors in the production of coma in myxoedema. The E.E.G. may be correlated with the changes in cerebral metabolism.

I thank Dr. R. W. Brookfield and Dr. R. R. Hughes, of the Royal Southern Hospital, and Dr. V. K. Summers, of Walton Hospital, for permission to publish cases under their care. The automatic frequency analyser used in this study was provided by the Research Committee of the United Liverpool Hospitals.

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VALUE OF THE VOICE IN DIAGNOSIS OF MYXOEDEMA IN THE ELDERLY*

BY

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Adult myxoedema was first described by Gull in 1874, and it was Ord (1878), who first called it myxoedema. In Allbutt's *System of Medicine*, first published in 1897, Ord gives a masterly description of a female case, and there have been numerous studies of this disease since that time (Report, 1888; Bramwell, 1892; Howard, 1907; White, 1913; McCarrison, 1917; Janney and Henderson, 1920; Lerman, 1937; Means, 1937; Rundle, 1951; Spence, 1953; Werner, 1955; Asper and Wiswell, 1956). There seems to be little disagreement that the classical case of myxoedema is easy to recognize, but the onset is insidious, and by the time the diagnosis is made the disease has often been present for years (Means, 1937). Myxoedema is apt to be overlooked as a cause of symptoms in those over the age of 60, if only for the fact that so many in this age group ascribe the symptoms to their advancing years and regard them as inevitable.

The symptomatology of myxoedema tends to be diffuse and equivocal. Most people over the age of 60 attending as hospital out-patients will, on questioning, admit to some symptoms commonly associated with myxoedema. These are: increasing weight, constipation, falling hair, sensitivity to cold, dry skin, difficulty in walking, vague limb pains, failing of memory and concentration, slow thought, and dizzy spells. Cases of myxoedema respond very well to adequate treatment with thyroid. This, coupled with the fact that untreated cases of myxoedema are unusually prone to death from infection and coma (Hadden, 1879; Report, 1888; Summers, 1953; Le Marquand *et al.*, 1953, 1955; Malden, 1955; Marshall and McCaughey, 1956; Surtees and Ginsberg, 1958; Emslie-Smith, 1958), makes early diagnosis important.

Almost all authors (Bramwell, 1892; White, 1913; McCarrison, 1917; Spence, 1953) mention the alteration of the voice that may occur with the development of the disease, but few stress its value, although Means (1937) states that "the voice change and speech peculiarities, taken together, form a combination almost pathognomonic of the disease"; and Asher (1949) has described the voice as being like a bad gramophone record of a drowsy, slightly intoxicated person with a bad cold and a plum in the mouth.

*Read at the meeting of the International Association of Gerontology, European Clinical Section, held at Sunderland General Hospital on October 2, 1958.

The purpose of this paper is to draw attention to the change in voice as an important clinical sign. In hospital practice during the past 15 months I have seen 22 cases of myxoedema. In five of these the voice change was for me the only striking sign of the condition.

The voice changes are divisible into two main groups, as follows.

1. *Alterations in Quality.*—The main voice changes are: (1) Low pitch. (2) An increased catarrhal or nasal quality. (3) A clotted quality—this can readily be simulated if a large quantity of sugary material, such as milk chocolate, is held and dissolved slowly in the mouth and swallowed after a few minutes: dysarthria is experienced and the voice sounds clotted. (4) Huskiness. (5) Harshness.

2. *Alteration in Diction.*—There is difficulty in articulation, and, as most authors point out, many patients with myxoedema speak slowly and deliberately and often have difficulty with certain words, which are stumbled over and slurred. Some, however, speak rapidly and in doing so are unable to retain the normal word spacing, so that slurring of groups of words occurs. Most patients who exhibit this slurring of groups of words usually show a mixture of rapid and slow diction. It is as though there is initially much inertia, and that this inertia is overcome with difficulty and the words then bubble out. This slurring is highly characteristic, and is unlike the slurring encountered in "drunks," who do not speak rapidly, and slurring, when it occurs, is over a single word and does not involve a group of words as it does in some cases of myxoedema. Patients with myxoedema who have been in the habit of singing often complain of their inability to sing after the onset of the disease (Granger, 1917) and note an alteration in pitch.

Any case of myxoedema may exhibit one or more of these characteristic changes.

Case 1

A man aged 69 was seen in the out-patient department in February, 1958. He complained of aching pains in his buttocks and thighs, swelling of his hands and face, general tiredness, and increasing weight for many years. Further questioning elicited that he was extremely sensitive to cold, had noticed paraesthesiae of the fingers of both hands, watering of his eyes with nasal catarrh, and increasing deafness. He had suffered from chronic bronchitis for many years, and since 1951 his weight had been recorded intermittently at a hospital department elsewhere. In October, 1951, he weighed 7 st. 12 lb. (50 kg.), in 1954 he was 8 st. 4 lb. (52.6 kg.). In February, 1958, he weighed 9 st. 4 lb. (59 kg.)

On examination the most striking thing about him was his voice, which I considered to be typical of myxoedema. It was husky and clotted, his diction was rather low, and he tended to slur groups of words. There was obvious dysarthria. The skin of his neck, hands, and forearms was dry. My notes at this time show that I thought his appearance was only "suggestive of myxoedema." His blood pressure was 150/55, pulse rate 64, and, apart from a few signs suggestive of chronic bronchitis, examination of his remaining systems did not show any abnormality. His haemoglobin was 109%. Serum proteins and liver-function tests were within normal limits. *X*-ray examination of his chest showed a normal heart outline and changes ascribed to chronic bronchitis. His E.C.G. was of a generally low voltage and compatible with the diagnosis of myxoedema. The thyroidal radio-iodine uptake was reported as 4% of the administered dose at 47 hours.

He was treated with increasing doses of thyroid, and after seven months he took 0.5 mg. of L-thyroxine daily and appeared to be well (Fig. 1). His voice was normal in quality and diction.

Case 2

A woman aged 72 was seen in the out-patient department in May, 1958. She had had unsteadiness and difficulty in walking for seven years, with vague pains in her back, chest, and limbs, and a burning sensation in her mouth and tongue. Further questioning elicited sensitivity to cold, lifeless falling hair, deafness, general tiredness, paraesthesiae of her fingers and feet, poor appetite with recent loss in weight, loss of singing voice, roughness and peeling of her

FIG. 1.—Case 1. Patient before and after treatment.

FIG. 2.—Case 2. Patient before and after treatment.

skin, and obstinate constipation over the past two or three years.

On examination the most striking feature, apart from pallor, was her voice, which was low-pitched and clotted, and her diction, which showed the characteristic slurring of groups of words. Mentally she was lively, witty, and intelligent, but was obsessed with her complaints. Her blood pressure was 170/90 and pulse 75; the cardiac impulse was impalpable and heart sounds were closed. There were changes in both knee-joints compatible with osteoarthritis.

Her thyroidal radio-iodine uptake was reported as 7% of the administered dose at 76 hours, haemoglobin 75%, red blood count 3,620,000, colour index 1.04, total white count 4,400 (polymorphs 51%, lymphocytes 49%).

She was treated with L-thyroxine, and after four months there was a striking change in her appearance (Fig. 2) and voice, the haemoglobin had risen to 95%, she walked more easily, was no longer sensitive to cold, and had lost her paraesthesiae and pains in the back, chest, and limbs, but was still far from satisfied with her response to treatment. She is now receiving 0.5 mg. of L-thyroxine daily.

Case 3

A man aged 68 first came under my care in January, 1957. He lived alone, and for six months before admission had complained of increasing difficulty in walking. Four weeks before admission he had taken to his bed and had become doubly incontinent. His main complaint, apart from being unable to walk, was sensitivity to cold. Examination revealed a grossly obese man. His blood pressure was 150/90, pulse 70, temperature 97° F. (36.1° C.). Cardiac impulse was impalpable, heart sounds were closed. His appearance, apart from some mooning of his face, did not suggest myxoedema, but his voice, which was low-pitched, husky, clotted, and harsh, and his diction, which showed slurring, were typical. At this time his haemoglobin was 86%. The E.C.G. showed sinus rhythm with flattening of T waves. The voltage appeared normal. *X*-ray examination of his chest showed changes thought to be due to chronic bronchitis. His heart size and outline appeared to be normal.

He was treated with dried extract of thyroid and was discharged home after six weeks in hospital. At this time, although there was little appreciable change in his voice, he had lost nearly a stone (6.4 kg.) in weight, was able to walk freely, had regained control of micturition and bowels, and was mentally much brighter. He was followed as an out-patient, but it soon became apparent that he was reducing the intake of thyroid: he complained that he felt peculiar after taking the tablets and that they were not doing him any good. His intake of thyroid from April, 1957, to March, 1958, is uncertain, but it is probable that he took only ½-gr. (32-mg.) tablets of thyroid intermittently from September, 1957.

He was readmitted in March, 1958, when his appearance, physically and mentally, were virtually the same as in January, 1957. His voice was low-pitched, clotted, and harsh, and at times almost unintelligible. His haemoglobin was 36%, with a normochromic normocytic picture. He was treated with L-thyroxine with considerable benefit, and after two months was well enough to go home. After seven months' treatment his haemoglobin, which had been slowly rising since treatment with thyroid was started, was 70%. His voice had lost most of its clotted, harsh quality and he was physically and mentally extremely active. His weight was 11 st. 5 lb. (72.1 kg.), compared with 13 st. 9 lb. (86.6 kg.) in January, 1957. He was receiving 0.4 mg. of L-thyroxine daily.

Case 4

A man aged 76 complained of anorexia, nocturia, loss of strength and appetite, sensitivity to cold, and pain in the lumbar region for two years. Questioning elicited a history of profuse watering of the eyes and nasal catarrh. He was said to have had inflammation of the kidney some 30 years previously, but no further details of this illness were available. Early in 1956 he had apparently had a left-sided hemiplegia, but had made a rapid and complete recovery. In October, 1956, suprapubic prostatectomy for benign prostatic hypertrophy had been carried out.

On examination he was pale, he looked anaemic, and there was well-marked pouching under both eyes. His blood pressure was 150/90 and pulse rate 70. Examination of his chest revealed signs suggestive of chronic bronchitis, but physical examination was otherwise negative. His voice was low-pitched, husky, and nasal; his diction was deliberate.

His history and complaints suggested that he was suffering from chronic pyelonephritis, although the quality of his voice and his diction suggested myxoedema. His haemoglobin was 80%; a mid-stream specimen of urine showed traces of albumin with a few hyaline casts, but was sterile on culture; and the blood urea was 27 mg. per 100 ml. His E.C.G. appeared to be within normal limits, and a thyroidal radio-iodine uptake was reported as 5% of the administered dose at 24 hours. He was treated with thyroid extract, and after 10 months there was an improvement in his appearance, voice, and symptoms, although his nocturia persisted. He was then receiving 0.5 mg. of L-thyroxine daily.

Case 5

A man aged 69 complained of having had bronchitis for 39 years, with swelling of his legs and shortness of breath on exertion for eight months. When first seen he was able to walk only a few yards on the flat before pausing for breath. He denied sensitivity to cold, although he admitted that his hands and feet were occasionally cold. He was much troubled with nasal catarrh and watering of the eyes. He had been treated for heart failure along the usual lines with no benefit.

On examination he was obese and had a rather sallow complexion. There was swelling of his periorbital tissues and marked pitting oedema of his legs, with increased filling of the neck veins. His blood pressure was 180/110, pulse 80 and irregular, the cardiac impulse was impalpable, and heart sounds were closed. His skin generally was dry and rough, this being most pronounced over the forearms, legs, and back. Examination of his chest showed only a few signs compatible with bronchitis.

At first sight he appeared to be a chronic bronchitic with hypertensive heart disease, but his voice was so low-pitched, nasal, and husky, and his diction so slow and deliberate, that the question of myxoedema complicating heart failure was considered.

E.C.G. showed auricular fibrillation with flattened T waves and a slight depression of the ST segment in the left ventricular leads. The haemoglobin was 82%, serum proteins 6.7 g./100 ml. (albumin 4 g., globulin 2.7 g.), and thyroidal radio-iodine uptake was 3% of the administered dose at 23 hours. Treatment was started with thyroid, ¼ gr. (16 mg.) twice daily, and over the next six months his daily dose was gradually raised to 3 gr. (0.2 g.) daily. By this time there was a considerable improvement in his appearance and manner, with lightening of his voice and speeding up of his diction. He indicated also that his exercise tolerance had increased, but the oedema of his legs persisted. His thyroid dosage was further increased, and chlormerodrin, one tablet three times a day, was added.

After 10 months' treatment he took 6 gr. (0.4 g.) of thyroid extract daily. He is over 1½ st. (9.5 kg.) lighter than when he first came to see me, is free from oedema, enjoys walking, and has started to sing again. His voice is higher-pitched and has lost all its catarrhal quality, and his diction is normal in speed.

Discussion

When these five cases were first seen the correct diagnosis was suggested by the voice. A comparison of

the photographs of Cases 1 and 2, before and after treatment, shows that, for one observer at least, gross facial changes produced by myxoedema can be overlooked. This was probably due to the fact that when the patients were first seen there was no standard of appearance against which to make comparison.

The voices of all these patients had changed as a result of disease, but again there was no pre-existing normal standard. The fact that the voice rather than the facial change was appreciated in these cases suggests that the voice change in myxoedema may be pathognomonic, as suggested by Means (1937). It would therefore seem to be a most important clinical sign. The most characteristic changes are an impression of dysarthria, slurring together of groups of words, and what I have called clotting of the voice. No amount of verbal description can adequately demonstrate these changes, but once they are appreciated they are readily recognized. Serial voice recordings, in my opinion, can take their place beside serial B.M.R.s and photographs as diagnostic aids in doubtful cases of myxoedema, as they have done in the five cases I have discussed.

Summary

Five cases of myxoedema in people over the age of 60 are described. In these cases recognition of the characteristic change in the voice led to the diagnosis. The importance of the voice changes in myxoedema in the elderly is stressed and an attempt is made to describe them.

It is a pleasure to record the help I have received in the preparation of this paper from Dr. Ian Goldberg, assistant pathologist to Oldham General Hospital; Mr. Peter A. D. McCarthy, department of phonetics, Leeds University; Mr. C. Richardson, department of photography, Oldham Royal Infirmary; and Miss Joyce Wynne, my secretary. The radio-iodine uptake tests were performed at the Christie Hospital and Holt Radium Institute, Manchester. The Hospital Management Committee have generously provided a tape recorder, which has enabled these voices to be studied.

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NICOUMALONE: A NEW ANTICOAGULANT

BY

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Assistant Pathologist, Whipps Cross Hospital, London

Dicoumarol was introduced in 1943 for the treatment of thrombosis, and in the ensuing years this form of therapy has become firmly established. The action of dicoumarol was slow and prolonged, and the search was continued for drugs which were more rapidly metabolized. The latest addition to this ever-lengthening list is nicoumalone ("sinthrome"), and an attempt is here made to evaluate its worth.

It is to be noted that initial and maintenance doses of nicoumalone used in this series are much lower than those recommended by American authors (Table I).

TABLE I

Author	No. of Patients	Method	Therapeutic Level	Dose of Nicoumalone	
				Initial	Maintenance
Walker (1955)	20	Quick's one-stage method	10–30% prothrombin activity	16–24 mg.	2–4 mg.
Long *et al.* (1956)	92	,, ,,	,, ,,	16–40 ,,	2–10 ,, (av. 5 mg.)
Neill *et al.* (1957)	156	Link and Schapiro's modification of Quick's one-stage	15–20% activity	28 ,,	5–9 mg.
Pratt (1956)	116	,, ,,	Prothrombin time of 25–32 secs.	12–32 ,,	4–12 ,,
Johnson *et al.* (1957)	50	Bedside method of Howell	40% of normal	20–28 ,,	2–6 ,,

These have ranged up to 40 mg. for the loading dose and from 2 to 12 mg. a day for maintenance. Their patients may have been kept nearer the limit of safety than our own patients. Nevertheless, I am of the opinion that a loading dose of over 20 mg. is unnecessary and may be dangerous. The drug is dispensed in 4-mg. tablets. This is not convenient, since 2-mg. and 3-mg. doses are often required.

Material and Methods

In the period August, 1957, to September, 1958, inclusive, 269 patients received this drug. These comprise 155 cases of coronary thrombosis, 107 cases of venous thrombosis, and 7 cases of arterial occlusion. As a routine, patients with coronary thrombosis were started on heparin and oral anticoagulant therapy simultaneously, the administration of heparin being terminated after 36 hours. The dose of oral anticoagulant was controlled by "prothrombin" estimations, using Quick's one-stage technique. Unless the case presented some special difficulty, these tests were done three times a week, the week-end doses being based on the Friday's results. Where the patient's reaction to the drug was abnormal (more or less sensitive) more frequent controls were made. Results were recorded as "percentage prothrombin activity," the figures being obtained by reference to a "prothrombin" dilution curve. The dose of the drug was prescribed by a member of the laboratory staff with ample experience of this form of therapy.

For comparison, a study was made of the records of 117 patients who received "indema" (phenindione) and

242 patients who were treated with "dindevan" (phenindione). In all these cases essentially the same procedure as detailed above was followed.

Results

Induction Therapy.—Early results indicated that a dose of 12 mg. on the first day and of 6–8 mg. on the second day were sufficient to depress the "prothrombin" to the desired level—20% activity (prothrombin time 39 seconds, compared with a control time of 13 seconds).

Maintenance Therapy.—The dose varied slightly from case to case, but was most often in the region of 2 to 3 mg. a day, given as a single evening dose. In more sensitive patients the occasional omission of a dose sufficed, and did not result in wide fluctuations of the "prothrombin" level.

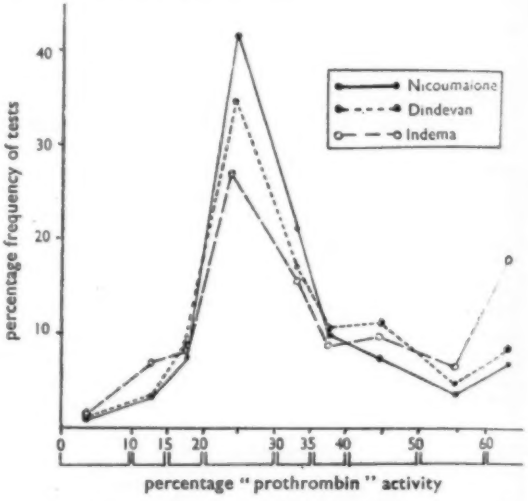
Recovery Phase.—In patients receiving maintenance therapy of 2–4 mg. a day, withdrawal of the drug resulted in a return to normal in 36 to 48 hours. In very sensitive patients this period might be longer, while in a few less-sensitive cases the return occupied no more than 24 hours.

Evaluation of the Drug

An attempt was made to compare the three drugs mentioned by studying the constancy of the "prothrombin" levels obtained during the period of maintenance therapy. To do this the results of all tests on patients receiving these drugs (excluding the period of induction and the last test) were collected and grouped as shown in Table II. The number in each group (columns e to o) was calculated as a percentage of the total number of tests in that particular series (column p), and these percentages were used to construct the frequency curve shown in the Graph.

The study includes 1,284 tests (column p) on 269 patients who received nicoumalone. Of these, 893 tests (69.8%) fall within the range 15–35% activity. Only 13 results (1%) occur in the less than 10% range, and 85 tests (6.6%) gave readings above 60%. Compared with this are 984 tests on 117 patients who received indema. Of these, 487 tests (49.3%) were within the range 15–35%, 15 (1.5%) were below 10%, and 175 (18%) were above 60%. There are also recorded 1,344 tests on 242 patients who received dindevan. Of these, 806 tests (60.1%) were within the 15–35% range, 16 (1.2%) were below 10%, and 111 (8.3%) were above 60%.

These figures are better appreciated when presented as a frequency curve (see Graph). The highest peak of incidence of tests within the range 15–35% occurs among those patients receiving nicoumalone, and the incidence of tests in the (undesirable) extreme ranges are also lowest in this group of patients.



Frequency curves with the three drugs.

Discussion

Since the introduction of dicoumarol in 1943 much effort has been directed towards producing an anticoagulant which approaches perfection. Such an ideal drug (1) should be rapid in action, but not dangerously so; (2) should be non-toxic and well tolerated; and (3) its action should be maintained for 24 hours, but not much longer: this will permit adequate control to be achieved on a single daily dose, and will reduce to a minimum any cumulative tendency, allowing normal values to be reached rapidly should the drug be withdrawn. Upon this activity–time relationship will turn the effectiveness of an anticoagulant in clinical practice, enabling the physician to maintain a stable "prothrombin" level with minimal fluctuation, thereby reducing the incidence of progressive thrombosis and of spontaneous haemorrhage.

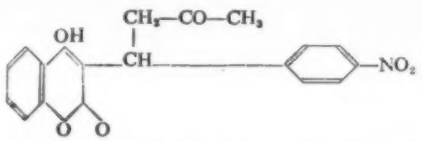
Reports of the use of nicoumalone have appeared from America (Pratt, 1956; Long *et al.*, 1956; Johnson *et al.*, 1957; Neill *et al.*, 1957) and Europe (Scardigli and Guidi, 1955; Moeschlin and Schorno, 1955;

TABLE II.—*Distribution of Tests Grouped in Relation to "Prothrombin" Levels*

Year	Drug	No. of Cases	No. of Patient-days	"Prothrombin" Levels—No. of Tests									Total No. of Tests
				<10%	10%–	15%–	20%–	30%–	35%–	40%–	50%–	60%+	
(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(k)	(i)	(m)	(n)	(o)	(p)
1958	Nicoumalone	182	2,373	7	21	52	320	176	56	52	18	41	743
1957	"	87	1,448	6	18	44	210	91	59	44	25	44	541
	Total	269	3,821	13 *(1·0)*	39 *(3·0)*	96 *(7·5)*	530 *(41·3)*	267 *(21·0)*	115 *(9·0)*	96 *(7·5)*	43 *(3·4)*	85 *(6·6)*	1,284 *(100·3)*
1957	Indema ..	117	1,638	15 *(1·5)*	66 *(6·7)*	77 *(7·8)*	260 *(26·3)*	150 *(15·2)*	87 *(8·8)*	92 *(9·4)*	62 *(6·3)*	175 *(18·0)*	984 *(100·0)*
1957	Dindevan ..	51	773	3	7	27	90	51	31	30	14	11	263
1956	" ..	191	3,092	13	37	91	371	177	130	117	45	100	1,081
	Total ..	242	3,865	16 *(1·2)*	44 *(3·3)*	118 *(8·8)*	461 *(34·3)*	227 *(17·0)*	161 *(11·9)*	147 *(10·9)*	59 *(4·4)*	111 *(8·3)*	1,344 *(100·1)*

The figures in italics represent percentages.

Montigel and Pulver, 1955). It is a coumarin derivative with the following formula:



Nicoumalone: 3-[α-(4′-nitrophenyl)-β-acetylethyl]-4-hydroxycoumarin.

Like other derivatives of coumarin its main action is to depress factor VII, and later, and to a less extent, prothrombin, though after several weeks of treatment both substances are equally affected (Moeschlin and Schorno, 1955).

It is not cumulative, and rapidly disappears from the body, being excreted unaltered in the urine.

It is of low toxicity in animals (Pratt, 1956), the mouse LD_{50} being 1,470 mg./kg. body weight compared with 270 mg./kg. in the case of dicoumarol. It is practically tasteless and is well tolerated by patients.

In this study no attempt has been made to assess the drug on purely clinical grounds—that is, incidence of deaths among patients with coronary artery disease, or the frequency of spontaneous haemorrhage. This omission has been allowed for two reasons. Firstly, because such statistics are often difficult to interpret and may be misleading (Honey and Truelove, 1957). Secondly, because it seems a reasonable deduction that the clinical results are but a reflection of the stability, or otherwise, of the "prothrombin" level during anticoagulant therapy. The patient with the "straight line graph" is less likely to suffer the hazards of extending thrombosis or dangerous haemorrhage than his less fortunate neighbour whose tests indicate widely fluctuating "prothrombin" levels from day to day.

Only two cases of severe spontaneous haemorrhage have occurred in this series of patients receiving nicoumalone. In one instance the patient exhibited abnormal sensitivity to the drug, a "prothrombin" activity of less than 10% being recorded after the patient had received a total of only 12 mg. in 48 hours. In the second instance melaena occurred in a patient with a history of probable gastric ulcer. In this case also the "prothrombin" activity was less than 10%.

The results recorded in Table II and in the Graph indicate that a high degree of stability of the "prothrombin" level may be anticipated with the use of nicoumalone. This is likely to be accompanied by an improved prognosis among patients with thromboembolic phenomena.

Conclusion and Summary

Nicoumalone, a new coumarin derivative, represents a step forward in the search for the ideal anticoagulant.

The stability of the "prothrombin" levels of 269 patients receiving nicoumalone is compared with the same in 117 patients receiving indema and 242 patients receiving dindevan. In this series the results with nicoumalone are superior to those obtained with the other two drugs.

The properties of this new anticoagulant are briefly reviewed.

My thanks are due to Dr. W. W. Walther for reading the manuscript and for his advice.

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MASS RADIOGRAPHY AND CANCER OF THE LUNG

BY

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During 1955, the last year for which national figures have been published, mass radiography units in England and Wales detected 1,482 cases of cancer of the lung and mediastinum (Ministry of Health, 1957a). National morbidity figures for new cases of cancer of the lung are not available, but the 17,272 deaths from cancer of the lung during that year (Ministry of Health, 1956) suggest that at present mass radiography does not find more than 10% of all new cases of cancer of the lung in England and Wales. It must be added that of the above figures almost half were not detected by conventional routine mass radiography, but at sessions for symptomatic cases referred by general practitioners, a type of service now widely employed by many units. The organization and deployment of the mass radiography units in the Birmingham Region have recently been described by one of us (McDowell, 1958).

The small contribution of the service to the finding of a highly fatal disease, such as carcinoma of the lung, is thought by many to be a major challenge. From the public health viewpoint the problem is, of course, entirely different from that of tuberculosis; the community derives no epidemiological benefit from finding cases of cancer whether they are curable or not, and the results are purely personal. Nevertheless, if it could be shown that mass radiography improves the prognosis for this disease by "early diagnosis" it could be argued that the present mass radiography policy needs revising and that an intensive national campaign for periodical chest *x*-ray examination of persons in the critical age groups is called for.

In the United States some workers believe mass radiography to be an effective method for finding cases with good chances of operability and survival (Overholt and

242 patients who were treated with "dindevan" (phenindione). In all these cases essentially the same procedure as detailed above was followed.

Results

Induction Therapy.—Early results indicated that a dose of 12 mg. on the first day and of 6–8 mg. on the second day were sufficient to depress the "prothrombin" to the desired level—20% activity (prothrombin time 39 seconds, compared with a control time of 13 seconds).

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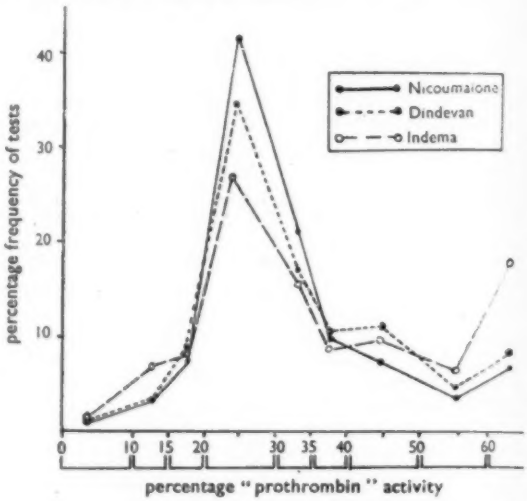

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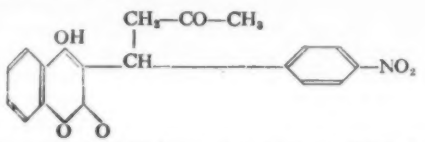
	Total	269	3,821	13 *(1·0)*	39 *(3·0)*	96 *(7·5)*	530 *(41·3)*	267 *(21·0)*	115 *(9·0)*	96 *(7·5)*	43 *(3·4)*	85 *(6·6)*	1,284 *(100·3)*
1957	Indema ..	117	1,638	15 *(1·5)*	66 *(6·7)*	77 *(7·8)*	260 *(26·3)*	150 *(15·2)*	87 *(8·8)*	92 *(9·4)*	62 *(6·3)*	175 *(18·0)*	984 *(100·0)*
1957	Dindevan ..	51	773	3	7	27	90	51	31	30	14	11	263
1956	,, ..	191	3,092	13	37	91	371	177	130	117	45	100	1,081
	Total ..	242	3,865	16 *(1·2)*	44 *(3·3)*	118 *(8·8)*	461 *(34·3)*	227 *(17·0)*	161 *(11·9)*	147 *(10·9)*	59 *(4·4)*	111 *(8·3)*	1,344 *(100·1)*

The figures in italics represent percentages.

Montigel and Pulver, 1955). It is a coumarin derivative with the following formula:



Nicoumalone: 3-[α-(4'-nitrophenyl)-β-acetylethyl]-4-hydroxycoumarin.

Like other derivatives of coumarin its main action is to depress factor VII, and later, and to a less extent, prothrombin, though after several weeks of treatment both substances are equally affected (Moeschlin and Schorno, 1955).

It is not cumulative, and rapidly disappears from the body, being excreted unaltered in the urine.

It is of low toxicity in animals (Pratt, 1956), the mouse LD_{50} being 1,470 mg./kg. body weight compared with 270 mg./kg. in the case of dicoumarol. It is practically tasteless and is well tolerated by patients.

In this study no attempt has been made to assess the drug on purely clinical grounds—that is, incidence of deaths among patients with coronary artery disease, or the frequency of spontaneous haemorrhage. This omission has been allowed for two reasons. Firstly, because such statistics are often difficult to interpret and may be misleading (Honey and Truelove, 1957). Secondly, because it seems a reasonable deduction that the clinical results are but a reflection of the stability, or otherwise, of the "prothrombin" level during anticoagulant therapy. The patient with the "straight line graph" is less likely to suffer the hazards of extending thrombosis or dangerous haemorrhage than his less fortunate neighbour whose tests indicate widely fluctuating "prothrombin" levels from day to day.

Only two cases of severe spontaneous haemorrhage have occurred in this series of patients receiving nicoumalone. In one instance the patient exhibited abnormal sensitivity to the drug, a "prothrombin" activity of less than 10% being recorded after the patient had received a total of only 12 mg. in 48 hours. In the second instance melaena occurred in a patient with a history of probable gastric ulcer. In this case also the "prothrombin" activity was less than 10%.

The results recorded in Table II and in the Graph indicate that a high degree of stability of the "prothrombin" level may be anticipated with the use of nicoumalone. This is likely to be accompanied by an improved prognosis among patients with thromboembolic phenomena.

Conclusion and Summary

Nicoumalone, a new coumarin derivative, represents a step forward in the search for the ideal anticoagulant.

The stability of the "prothrombin" levels of 269 patients receiving nicoumalone is compared with the same in 117 patients receiving indema and 242 patients receiving dindevan. In this series the results with nicoumalone are superior to those obtained with the other two drugs.

The properties of this new anticoagulant are briefly reviewed.

My thanks are due to Dr. W. W. Walther for reading the manuscript and for his advice.

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MASS RADIOGRAPHY AND CANCER OF THE LUNG

BY

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During 1955, the last year for which national figures have been published, mass radiography units in England and Wales detected 1,482 cases of cancer of the lung and mediastinum (Ministry of Health, 1957a). National morbidity figures for new cases of cancer of the lung are not available, but the 17,272 deaths from cancer of the lung during that year (Ministry of Health, 1956) suggest that at present mass radiography does not find more than 10% of all new cases of cancer of the lung in England and Wales. It must be added that of the above figures almost half were not detected by conventional routine mass radiography, but at sessions for symptomatic cases referred by general practitioners, a type of service now widely employed by many units. The organization and deployment of the mass radiography units in the Birmingham Region have recently been described by one of us (McDowell, 1958).

The small contribution of the service to the finding of a highly fatal disease, such as carcinoma of the lung, is thought by many to be a major challenge. From the public health viewpoint the problem is, of course, entirely different from that of tuberculosis; the community derives no epidemiological benefit from finding cases of cancer whether they are curable or not, and the results are purely personal. Nevertheless, if it could be shown that mass radiography improves the prognosis for this disease by "early diagnosis" it could be argued that the present mass radiography policy needs revising and that an intensive national campaign for periodical chest *x*-ray examination of persons in the critical age groups is called for.

In the United States some workers believe mass radiography to be an effective method for finding cases with good chances of operability and survival (Overholt and

Schmidt, 1949; Guiss, 1952; Rigler *et al.*, 1953; Overholt *et al.*, 1955), but other American authors take a rather pessimistic view (Ehler *et al.*, 1954; Boucot and Sokoloff, 1954; McNulty, 1954).

In this country little information about the fate of cancer cases found by mass radiography is available. The allegedly better prognostic chances for such cases have so far been deduced from very small numbers only (Nicholson *et al.*, 1957).

A follow-up study of a large number of cases discovered by mass radiography seemed therefore desirable, and since July, 1955, we have been collecting information about all such cases in the Birmingham Region. The present contribution deals with 238 out of 240 male cases found by six mass radiography units of the Birmingham Regional Hospital Board in the twelve months following July 1, 1955, whose fate had been traced by the Regional Cancer Registry after twelve months.

This paper compares cases found by conventional routine mass radiography and patients referred to the units by general practitioners. The main point of interest is a comparison of resectability rates between these two groups. In the course of the investigation we found much confirmatory evidence of certain aspects of the disease, published by other authors, particularly with regard to age-and-sex distribution, histological types, and smoking habits. In these respects we do not claim to contribute anything new, and relevant data are shown only in their relation to the main subject of interest.

The number of female cases found during the period under review was too small to give useful statistical information, and the paper deals therefore only with men.

Methods of Investigations

Basically all units followed the usual mass radiography procedure and used the 35-mm. film. In addition we recorded on specially designed forms information about area of residence, occupational histories, tobacco habits, principal and first clinical symptoms, the time of first consultation with general practitioners, and radiographic characteristics. All records were statistically analysed centrally by one of us (K.W.C.).

The methods of further investigations varied slightly from unit to unit. Generally speaking, cases with suspected neoplasms were referred to thoracic surgeons direct, but in a number of cases patients were first seen by chest physicians. A few patients, in whom further investigations established cancer of the lung, were referred from the M.M.R. unit with a preliminary diagnosis other than malignant disease, mostly pneumonitis, post-pneumonic or tuberculous pleural effusion, pulmonary tuberculosis, or progressive massive fibrosis.

Criteria of Diagnosis.—We included in the analysis only such cases where the diagnosis was either established by bronchoscopy, biopsy, cytological or histological examination, or necropsy (established cases), or where in the absence of such evidence two independent sources agreed that the course of the disease left no reasonable doubt about its nature (corroborated cases). The proportion of established to corroborated cases was 4:1, and it seems highly unlikely that this series includes a statistically significant number of misdiagnosed cases.

General Background of Investigation

Tables I and II show the findings of the six units during the calendar year 1956. This period was chosen because age and sex specific information of the number of examinees was easily available from the sample of M.M.R. returns analysed by the Registrar-General. The differences between the actual number of cases found during the year (277) and that of cases under review (240) in no way affect the following argument.

Table I, which includes all men above the age of 15, clearly shows that the number of cases found by each individual unit depended largely on the nature of its work. The Birmingham Static Unit, for instance, which discovered almost half of all cases, examined a high proportion of general-practitioner cases. For all units the case-finding rates for general-practitioner patients was 29 times as great as for volunteers at routine surveys, thus emphasizing the high selection of general-practitioner referrals.

TABLE I.—*Cases of Carcinoma of Lung in Men Discovered by Mass Radiography in Birmingham Region in 1956*

Unit	General-practitioner Referrals			Routine Surveys			All Men		
	X-rayed	No. of Cases	Rate per 1,000	*X*-rayed	No. of Cases	Rate per 1,000	*X*-rayed	No. of Cases	Rate per 1,000
Birmingham static	14,190	146	10·3	19,140	3	0·2	33,330	149	4·5
,, mobile	2,810	19	6·8	36,460	13	0·4	39,270	32	0·8
Stoke-on-Trent	3,200	16	5·0	39,320	14	0·4	42,520	30	0·7
Wolverhampton	2,820	20	7·1	27,420	6	0·2	30,240	26	0·9
Dudley	2,230	17	7·6	17,970	5	0·3	20,200	22	1·1
Coventry	460	5	10·9	33,300	13	0·4	33,760	18	0·5
All units	25,710	223	8·7	173,610	54	0·3	199,320	277	1·4

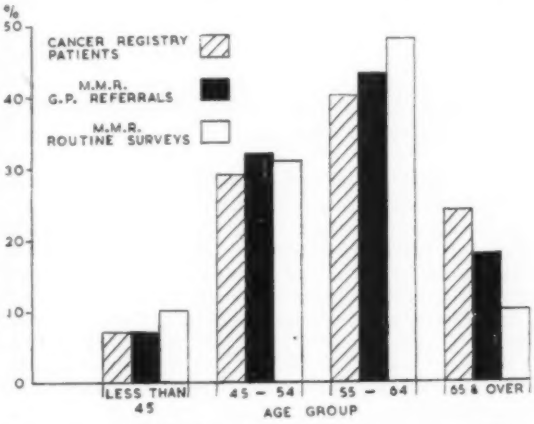
TABLE II.—*Age Distribution of Males with Carcinoma of Lung Discovered by M.M.R. Units in Birmingham Region during 1956*

Age Group	General-practitioner Referrals			Routine Surveys			All Men		
	No. of Examinees	No. of Cancer Cases	Rate per 1,000	No. of Examinees	No. of Cancer Cases	Rate per 1,000	No. of Examinees	No. of Cancer Cases	Rate per 1,000
<35	9,860	3	0·3	98,320	1	0·0	108,180	4	0·0
35–	5,390	16	3·0	34,060	3	0·1	39,450	19	0·5
45–	4,850	70	14·4	24,270	15	0·6	29,120	85	2·9
55–	2,080	41	19·7	8,520	15	1·8	10,600	56	5·3
60–	1,780	50	28·1	4,900	9	1·8	6,680	59	8·8
65+	1,720	43	25·0	3,390	11	3·2	5,110	54	10·6
All ages	25,680	223	8·7	173,460	54	0·3	199,140	277	1·4

The age of 180 examinees was not stated.

Results

Age Distribution.—In the Chart comparison is made between the age distribution of the 238 cases in this series and of 824 men suffering from cancer of the lung and registered from all sources with the Regional Cancer



Percentage age distribution of male lung cancer cases. Mass radiography cases and patients registered with the Birmingham Regional Cancer Registry in 1956.

Registry in Birmingham in 1956. It is clear that the age distribution of both our groups is fairly typical for the region as a whole, with the exception of a slight deficiency of mass radiography cases in the oldest age group.

TABLE III.—*Current Smoking Habits of Cancer Cases and of Male Population in the Midlands (Percentage Distributions)*

Group	Non-smokers	Cigarettes Consumed per Day			Total
		<15	15–24	>24	
G.P. referrals ..	6·4	21·6	43·3	28·7	100·0
Routine surveys	7·3	24·4	41·5	26·8	100·0
All cancer cases	6·6	22·2	42·9	28·3	100·0
Male population in Midlands	29·1	38·5	25·3	7·1	100·0

TABLE IV.—*Distribution of Cases According to Predominant Cell Type (Percentage Distributions)*

Group	Squamous	Undifferentiated	Adeno-carcinoma	Others	All Cases with Known Type
G.P. referrals ..	62·1	31·1	3·9	2·9	100·0 (103)
Routine surveys	51·9	33·3	3·7	11·1	100·0 (27)
Both sources ..	60·0	31·5	3·9	4·6	100·0 (130)

Smoking Habits.—Table III shows the low proportion of non-smokers in both groups of cancer patients. Amounts of tobacco consumed by pipe or "mixed" smokers have been converted into their cigarette equivalents in accordance with the usual formula. The close agreement between smoking habits in these two entirely different groups should be noted if only to emphasize the striking difference in smoking habits between the cancer cases and a cross-section of the male population in the Midlands (Cross *et al.*, 1958) after standardization with respect to age.

Histological Cell Type.—A histological diagnosis became available in 130 (55%) of all cases, which is slightly lower than the histological confirmation rate (62%) reported by Bignall (1958a) in a larger series from two London hospitals. In Table IV we attempted to group these cases on the lines suggested by Hinson (1958). This was possible in all but six cases, which are shown as "others." The group of "undifferentiated neoplasms" includes the oat-cell type. The table suggests a close similarity of the histological pattern in both groups, although the numbers of routine survey cases are rather small. Because of the lack of uniform reporting on histological specimens and of the different pathological material used in other investigations, comparisons with results elsewhere are difficult. Approximately 60% of our histological reports were based on resection specimens, and the proportion of types in this series is very similar to the distribution of cell types in resection specimens reported from two neighbouring regions (Nicholson *et al.*, 1957; Gifford and Waddington, 1957).

Twelve Months' Survival, Irrespective of Treatment.—Twelve months after attendance at the M.M.R. units 69 general-practitioner cases and 24 routine cases were still alive. The first-year survival rate of the latter group (50%), therefore, considerably exceeded that of the general-practitioner cases (36%), although the difference between the two rates was not statistically significant. The survival experience for both groups together (39%) was slightly higher than that of patients at two London hospitals (30%) reported by Bignall (1958b). Bignall's results are, however, not strictly comparable with this series, as his survival rates were calculated from first attendance at hospitals, which is not the same as first attendance for *x*-ray examination.

Resectability

Of all cases from both groups, 33% had a pneumonectomy or lobectomy (Table V). The rate was higher in the routine survey group (44%) than among general-practitioner patients (30%). The precise number of purely palliative resections (Abbey Smith, 1957) is not known, but is likely to have been small. It cannot have improved the resectability rates for routine survey cases, as the proportion of lobectomies in this group was much higher than for general-practitioner patients. We attach some importance to the high proportion of lobectomies in the routine survey cases, in view of the significance of this operation not only with regard to survival but also to post-operative disability (Bignall and Moon, 1955; Belcher, 1956; Cleland, 1958a).

Because of the many varying factors, to mention only different selection of cases by different surgeons, a true comparison of resectability rates between various

TABLE V.—*Resectability of M.M.R. Cases*

Group	Total No. of Cases	Pneumonectomies		Lobectomies		All Resections	
		No.	% of Total	No.	% of Total	No.	% of Total
G.P. referrals ..	190	41	21·6	16	8·4	57	30·0
Routine surveys	48	8	16·7	13	27·1	21	43·8
Total ..	238	49	20·6	29	12·2	78	32·8

TABLE VI.—*Deaths Within 2-Months and 12-Months Survival After Resection*

Group	Total No. of Cases	Patients Dying within 2 Months	Patients Alive 12 Months after Operation
G.P. referrals	57	4 (7·0%)	35 (61·4%)
Routine surveys	21	3 (14·3%)	10 (47·6%)
Total	78	7 (9·0%)	45 (57·7%)

TABLE VII.—*Resectability by Age*

Group	Under 45 Years			45–54 Years			55–64 Years			65 Years and Over			All Ages		
	All Cases	Resections		All Cases	Resections		All Cases	Resections		All Cases	Resections		All Cases	Resections	
		No.	%		No.	%		No.	%		No.	%		No.	%
G.P. referrals	14	3	21·4	60	27	45·0	82	25	30·5	34	2	5·9	190	57	30·0
Routine surveys	5	1	20·0	15	6	40·0	23	12	52·2	5	2	40·0	48	21	43·8
Total	19	4	21·1	75	33	44·0	105	37	35·2	39	4	10·3	238	78	32·8

thoracic centres is notoriously hazardous. We were interested to find that the resectability rates not only of our routine survey cases but also of general-practitioner patients were substantially higher than the corresponding rates of 19% for 748 male and female cancer cases diagnosed at the Birmingham United Hospitals in 1952 (United Birmingham Hospitals, 1954). The resectability rate reported from two London hospitals (Bignall, 1958c) was 23%, which is slightly lower than that for our general-practitioner patients and appreciably lower than for our routine survey cases.

Of the resected cases in both groups, 58% were alive 12 months after operation (Table VI). The number of resected routine cases is rather small, and no importance can therefore be attached to the higher survival rates of general-practitioner patients. The proportion of deaths within the first two months after operation (9%) was very similar to that reported by Cleland (1958b) for male patients at the Brompton Hospital between 1944 and 1955.

Factors Affecting Resectability

Age.—The very similar age distribution of cases in both our groups is shown in the Chart. The numerical excess of men over 65 years old in the general-practitioner group is, however, important, as in this age group only 4 out of 39 men were considered suitable for surgery (Table VII). This poor resectability rate lowered the proportion of resections for the group of general-practitioner patients as a whole. In the age group 55–64 years the proportion of routinely examined men who were resected was much higher than that for general-practitioner cases. The low resection rates for men below the age of 45 should be noted.

Histological Type.—The resectability rates for 124 cases of the squamous, undifferentiated, and adenocarcinoma types of neoplasm are shown in Table VIII.

TABLE VIII.—*Resectability by Histological Type*

Group	Squamous			Adenocarcinoma			Undifferentiated		
	No. of Cases	Resected		No. of Cases	Resected		No. of Cases	Resected	
		No.	%		No.	%		No.	%
G.P. referrals	64	39	60·9	4	2	50·0	32	11	34·4
Routine surveys	14	8	57·1	1	1	100·0	9	7	77·8
Total	78	47	60·3	5	3	60·0	41	18	43·9

In accordance with common experience (Bignall, 1958d; Nicholson *et al.*, 1957) squamous neoplasms proved generally to be more resectable than the undifferentiated tumours. As the numbers in each subgroup of the routine survey cases are small, comparison between the two groups is difficult, but it is worth while pointing out that the proportion of squamous-cell tumours in the routine survey group was smaller than among general-practitioner cases (Table IV).

Diagnostic and Therapeutic Delays

Ideally the prognostic significance of early or late diagnosis and treatment should be measured from the onset of first warning symptoms specifically related to the disease. The average duration of symptoms before diagnosis is usually given as four to six months (Taylor and Waterhouse, 1950; Brooks *et al.*, 1951; Thomas, 1952; Nicholson *et al.*, 1957); but, like Bignall (1958e), we have good reason to believe that the histories collected in this respect from our patients were in many instances very inaccurate and too unreliable for statistical evaluation.

Well-remembered incidents such as haemoptysis were present in only 19% of all cases and a febrile attack in only 8%. The main symptoms were cough and dyspnoea—36% and 34% respectively—and usually not even an approximate date could be recorded for the onset or change in character of these symptoms, which are common afflictions in the male population of this highly industrialized and air-polluted area, where approximately 70% of men are cigarette smokers (Cross *et al.*, 1958).

For most general-practitioner referrals we were, however, able to measure with reasonable accuracy the period between the patients' first visit to their doctors and their attendance at the M.M.R. unit. These "general-practitioner–*x*-ray intervals" are shown in Table IX.

TABLE IX.—*Resectability According to Interval Between Consulting G.P. and X-ray Examination*

Interval between G.P. Consultation and *X*-ray Examination	No. of Patients	% of Total	% Resected
Less than 1 month	68	35·8	22·1
1–2 months	62	32·6	29·0
3–4 ,,	23	12·1	43·5
5 months and over	12	6·3	(16·7)
Not recorded	25	13·2	
Total	190	100·0	

In recent years the controversial question of gross delay in diagnosis and treatment of lung cancers has often been raised in the medical press (Lutwyche, 1956; Thompson, 1957; d'Abreu and Taylor, 1957), and we believe it important to point out that at least two-thirds of general-practitioner cases were referred to us for *x*-ray examination within the first two months of consultation with their doctors and more than one-third within the first month. It is possible that the easy and direct access to chest *x*-ray facilities open to general practitioners in the Birmingham Region at M.M.R. units contributed to the early referrals of cases for *x*-ray examination.

The "*x*-ray–resection" intervals are shown in Table X. Only 18% of all cases were operated on within the

TABLE X.—*Interval Between X-ray Examination and Resection*

Interval between X-ray Examination and Resection	No.	% of Total
Less than 1 month	14	17·9
1- month	38	48·7
2- months	13	16·7
3- ,, ...	6	7·7
5 months and over	7	9·0
Total	78	100·0

first month after *x*-ray examination, but 67% within the first two months. As the patients were under our control for only three or four days, the time between miniature and full-size films, we do not feel in a position to comment on the reasons for delay in treatment. Obviously very complex and often unavoidable causes contribute to this delay, to mention only the reluctance of patients to accept thoracotomy. Generally we feel that the figures in Table X give no cause for dissatisfaction. Furthermore, taking the "general-practitioner–*x*-ray" interval as an index of delay, the data in Table IX do not show a direct relation between early referral and increased resectability. In fact, the highest resectability rates were found in men who were referred three to four months after consulting their doctors, and the rates for patients referred within the first month were much lower. This seems to confirm the findings of others (Bignall and Moon, 1955; Gifford and Waddington, 1957) that the duration of symptoms is not a reliable prognostic factor and that patients with long histories may fare better than those with very short ones.

Asymptomatic Cases

A case was classified asymptomatic if, after careful inquiries, neither the director of the M.M.R. unit nor the thoracic surgeon or chest physician to whom the patient was referred elicited significant symptoms in the man's history. There were only seven such cases, or 15% of the routine survey group. Naturally all the general-practitioner referrals had symptoms. These findings are in accordance with those of Boucot and Sokoloff (1954), who found only seven truly asymptomatic cases out of 77 discovered at mass radiography surveys in the United States. Of our seven cases, three had lobectomies and a fourth had a pneumonectomy.

The radiographic manifestations of "silent" cancers of the lung have been described as small peripheral coin lesions, small areas of atelectasis, obstructive localized emphysema, or linear atelectasis (Rigler *et al.*, 1953). Kerley (1958) believes that the chances of successful surgical removal of neoplasms presenting as small peripheral shadows are good.

We consider it important to stress that in this small group of seven silent tumours five cases presented with increased hilar shadows or opacities close to the pulmonary roots, one with a pleural effusion, and one with a large peripheral ring shadow. The smallest shadow was 2 by 2 in. (5 by 5 cm.) on a 12- by 15-in. (30- by 38-cm.) film. Small peripheral coin shadows were therefore entirely absent in this group.

Discussion and Conclusions

Statistical evidence of the small chances of influencing the course of lung cancer (Bignall, 1958f) is indeed overwhelming. On the other hand, Ellman's (1952) statement that "mass *x*-ray examination of the chest offers the best known single means of detecting, as rapidly and economically as possible, significant intrathoracic lesions in presumably healthy subjects" is now generally accepted.

The present series is to our knowledge the largest analysis of lung cancer cases found by mass radiography in this country, but we cannot claim that this contribution gives a clear-cut answer to the question of the value of mass radiography in the detection of this disease. We are also aware that a follow-up period of twelve months is short; but the investigation is continuing, and in future we hope to present data of survival after subsequent periods. Because of the widely accepted belief that early diagnosis can increase the chances of surgery (Bignall, 1958f) and diminish the number of those who arrive at thoracic surgeons only in the last stage of their illness (d'Abreu and Taylor, 1957), an analysis of resectability in cancer patients found by mass radiography seems to us important at the present time.

On the positive side we found a higher resectability rate in cases found at routine surveys as compared with cases referred by general practitioners because of symptoms. The difference, however, is small and not statistically significant. In a number of cases the fate of the patient was governed by factors of age, histology, acceptance, or refusal of operation—factors which are little or not at all related to early diagnosis. The 12-months-survival rate, irrespective of treatment, was higher for routine survey cases than for general-practitioner patients. This proves that other factors than resectability played an important part in prognosis.

The relatively large proportion of lobectomies in the routine survey group is encouraging, and it also seems that the resection rates for general-practitioner cases were higher than those for patients referred to the United Birmingham Hospitals from other sources.

On the negative side the most disturbing finding, to our minds, was the very small number of truly "silent" lesions, a strong reminder of the difficulties of early radiological diagnosis of lung cancer. Although we believe that since the inception of this investigation our threshold of suspicion has been raised, we do not know how many shadows due to cancer were missed during the period under review. Also, the number of men who attended our surveys, in whom the disease was already established but would not have shown on films of any size, is an unknown factor.

We agree with Kerley (1958) that part of the failure to detect a larger number of silent cancers may be due to radiographic technique, and that very small peripheral lesions are often not distinct enough on the 35-mm. film to be noted even by very experienced observers. It also seems reasonable that, in any surveys concerned with the early detection of cancer, dual independent reading is an essential prerequisite.

At present, both cancer of the lung and active tuberculosis are found predominantly in men above the age of 35, and it is on these age groups that the main effort of mass radiography should be concentrated.

In our opinion, regional hospital boards should implement, with a sense of urgency, the recent circular of the Ministry of Health (1957b) which called for an increase in static mass radiography facilities. The recommended use of the 100-mm. camera unit, with its larger film format and surperior quality of film, would make interpretation easier and more reliable. Dual

reading, which has proved to be impracticable in conventional mobile mass radiography, would present relatively little difficulty at static units with 100-mm. cut films. It is obvious that even a large number of these static units would be unable to deal with the periodical routine *x*-ray examination of all men in the critical age groups, but general practitioners could help by sending for chest *x*-ray examination all men over 35, irrespective of the reasons for visiting their surgeries.

In the meantime, it would be wrong in our opinion to engage in any form of propaganda that suggests that at present routine mass radiography is a certain means of detecting "early cancer," and attention should not be deflected from the much more important preventive aspects of the present situation.

Summary

A series of 238 cases of cancer of the lung in men found by mass radiography in the Midlands are reviewed. Comparisons are made between cases found by conventional routine mass radiography and patients referred to the units by general practitioners.

The 12-months-survival rates irrespective of treatment and the resection rates were higher for routine survey cases than for general-practitioner referrals. A larger proportion of routine survey cases had a lobectomy than general-practitioner patients. Various aspects and reasons for these differences are discussed.

Symptomatic cases were referred by general practitioners generally without undue delay, and the majority of resections were carried out within the first two months after *x*-ray examination.

The very small number of truly asymptomatic cases and the absence of small peripheral shadows in this series are discussed in their relation to future mass radiography policy.

The installation of more 100-mm. *x*-ray units to deal with a larger number of general-practitioner referrals, particularly of men in the critical age groups, is suggested.

ADDENDUM: Second-year Survival Rates.—Since this paper was written a second-year follow-up report has been obtained on all but three patients (two general-practitioner referrals and one routine survey case) of the 238 in the series. Assuming all three had died, there were 38 general-practitioner referrals and 12 routine survey cases alive two years *after the date of x-ray examination*. Hence the second-year survival rates regardless of treatment for the two survey groups were respectively: G.P. referrals, 20%; routine survey cases, 25%. The rate for all patients was 21%. Of the 57 general-practitioner cases and 21 routine survey patients resected, 25 and 8 respectively were alive two years *after the date of operation*. Hence the second-year survival rates for the two groups of patients were respectively 44% and 38%, and for both groups combined 42%.

We are indebted to the chest physicians and thoracic surgeons in the region for their full co-operation in providing information of patients referred to them. We are grateful to Miss J. M. Levi, of the Birmingham Regional Cancer Registry, for obtaining follow-up details of our patients; to Mrs. M. Sheldon and Miss A. Holdsworth for clerical assistance, and to Miss J. Yates for help with processing of the material.

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KALA-AZAR OF UNUSUAL DURATION, ASSOCIATED WITH AGAMMAGLOBULINAEMIA

BY

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The case here reported is of extraordinary duration in that over ten years must have elapsed between the last possible date of infection with *Leishmania donovani* and ultimate diagnosis. It is of further interest because the serum gamma-globulin was abnormally low, and because the patient finally developed secondary amyloidosis.

Case Report

An unmarried Pole aged 31 was admitted to the Royal Hampshire County Hospital, in the care of Dr. W. D. Brinton, in November, 1956, with the following history. He was born in 1925, and had lived and worked on the family farm near Cracow until taken to Austria in 1941, where he worked on farms near Klagenfurt for nearly four years. In 1945 he went to Italy, where he lived for 18 months in camps in the Bqlogna region; he mentioned Monte Prandone and San Giuliano particularly, and Budrio, a town of some size, ten miles (16 km.) east of Bologna. In the autumn

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of 1946 he came to England, and has remained here ever since, doing heavy manual work. He had not regarded himself as ill at any time, nor any member of his family as particularly susceptible to infectious diseases. He had, however, been in hospital twice during his ten years in this country.

In July, 1950, he was admitted with delayed healing following a dental extraction. Evening pyrexia, granulopenia, and enlargement of the liver to three fingerbreadths below the costal margin were noted. Jaundice developed and lasted one week. The laboratory investigations supported a diagnosis of infective hepatitis. The W.R. was negative. In September, 1950, he looked well, and the granulopenia and liver-function tests were improving. He returned to work, his weight being 9 st. 5 lb. (59.4 kg.).

His next admission to hospital was in December, 1955. He complained of excessive sweating, chiefly at night, and anorexia for the previous month, following a cough and epistaxis. A few superficial lymph nodes were palpable, as was the spleen, but the liver was not enlarged. The blood pressure was 140/70. All blood cultures, skin tests, agglutinations, and W.R. were negative, but a diagnosis of brucellosis was made, and was supported by an apparent response to chlortetracycline (total dosage 16 g.); the temperature fell to normal, and the spleen diminished in size. After one month in hospital he was discharged; he weighed (as before) 9 st. 5 lb. (59.4 kg.), and returned to heavy work.

In November, 1956, he was admitted as an emergency case, having fainted at work. He said that increasing ill-health and weakness had followed a sore throat two months previously. He had also suffered a moderate laceration of the left hypothenar eminence, which had been sutured, and for which he had been given prophylactic antitetanus serum ten days previously. On examination he was found to be emaciated and febrile (100° F.—37.8° C.), with a moderately enlarged soft spleen, and the edge of the liver was only just above the level of the umbilicus. Blood pressure was 110/70, pulse 90, and weight 7 st. 11 lb. (49.4 kg.). His face, however, looked "healthy" and was well coloured. Although muscular wasting was present in all groups, it was most pronounced in the upper arms. Alopecia was noted in patches on the head and legs. Leucopenia was more pronounced than formerly. Blood cultures, W.R., and agglutinations were again negative.

Kala-azar was specifically discounted at this time because of the length of time since possible infection and also a negative formol-gel test, and a diagnosis of histoplasmosis or toxoplasmosis was thought more probable. Sternal marrow smears showed an active normoblastic erythropoiesis; the granular series was chiefly represented by rather fragile myelocytes, many of which were apparently disrupted in spreading, and few mature forms. Few monocytes, lymphocytes, or plasma cells were seen, and all were mature forms. Platelet production appeared normal. Numerous parasites were seen, mostly intracellular in sections; few were so in the smears, possibly due to the trauma of spreading. The organisms were of about the same size as platelets, and presented a cigar-shaped appearance in the thicker parts of the smears, somewhat similar to *Toxoplasma gondii*. The characteristic appearances of *L. donovani*, with trophonucleus and kinetoplast, were present, however, and were identified by Dr. H. T. Findlay. Cultures were unfortunately overgrown by contaminants. The formol-gel test was still negative, as was the urea-stibamine test. Total protein in the serum was 4.1 g./100 ml. Paper electrophoresis showed a slight diffuse increase in the $alpha_1$ position and some decrease in albumin. The peripheral blood showed a reticulocytosis of 7% and haemoglobin of 68% (10.2 g./100 ml.).

Treatment was instituted with 15 daily intramuscular injections of 200 mg. of pentamidine isethionate (4:4'-diamidinodiphenoxypentane di - beta - hydroxyethane - sulphonate). This caused considerable local inflammation and pain, and almost certainly prolonged the pyrexia, but the spleen began to diminish in a few days. Owing to the apparent lack of effect of the drug on the temperature, the patient was transferred temporarily to the Hospital for Tropical Diseases, in the care of Professor A. W. Woodruff. While there the patient became afebrile, and absence of gamma-globulin was noted on paper electrophoresis. No further anti-leishmanial treatment was given, and the patient returned to the Royal Hampshire County Hospital.

Four weeks after the end of the pentamidine course he had gained 15 lb. (6.8 kg.). The white cell count was increasing; all tests for increased haemolysis were negative. The spleen was not palpable, but the liver was still enlarged to four fingerbreadths below the costal margin. Proteinuria was noted for the first time, but there were no casts or cells in the urinary deposit. Blood pressure was 140/80. The Congo-red test showed only 17% retention of dye in the plasma at one hour, when 60% or more might be expected in a healthy individual. The patient's serum agglutinated A and B red cells—which were agglutinable by control sera to titres of 1/128 and 1/256—only to titres of 1/8 and 1/4 respectively (patient's red cells were group O). It was not considered necessary to investigate adrenal cortical function at this time, as there had been no generalized increase in pigmentation, the blood pressure had returned to the 1955 level, and the serum chloride was within normal limits (104 mEq/l.; 608 mg./100 ml.). The 24-hour output of neutral 17-ketosteroids was 4.9 mg. (normal for an adult male, 9–14 mg.).

During the next four months the patient's weight increased to 10 st. 4 lb. (65 kg.), and he returned to work. By the end of May, 1957—that is, five months after the end of the pentamidine course—it was clear that some of the earlier improvement was not maintained, and one month later fever had returned and the patient's weight had fallen to 9 st. (57 kg.). The liver and spleen did not appear to have changed in size during the relapse. It was not thought advisable to repeat the Congo-red test in view of the potential danger (MacCuish, 1957). A second course of pentamidine was therefore given, in the same dosage as before, but intravenously. No unpleasant effects followed administration and he improved clinically for a few months, but proteinuria continued, and as the liver and spleen remained large and firm it was thought that amyloid disease had developed. This was not proved until March, 1958, when the patient was readmitted to the Hospital for Tropical Diseases, in the care of Professor A. W. Woodruff.

Discussion

It is often said that kala-azar should not be diagnosed in an illness that has lasted longer than 18 months. But unusually long incubation periods are reported by Sweeney, Friedlander, and Queen (1945), Norman (1946), Stone, Tool, and Pugsley (1952), and Jopling (1955); all these cases became ill two to three years after possible infection, and Mu and Huie (1929) refer to durations of one month to four years. Napier (1922) mentions four cases of more than five years' duration. The only recorded case (Castorina, 1924) of even longer duration is that of an Italian child of 7, who died a proved case with a compatible history since the age of 6 months. Castorina also mentions another boy of 11 in whom the disease had lasted seven years, but in this latter case the presence of the parasite was never proved.

The above patient's spleen was not palpable in 1950. His fever has never shown the classical double daily rise, nor has the blood pressure been recorded below 110/70. There has been progressive anaemia, presumably haemolytic in type; for before treatment in December, 1956, there was a reticulocytosis of 7%, with rapid improvement after pentamidine. Ascites was never present. Anorexia was present only during pyrexia.

Epistaxes occurred in 1955. Diarrhoea was troublesome in December, 1956, prior to treatment; no other specific cause was found. An irritating cough with little sputum was complained of in 1955 and 1956; Napier (1951) states that such a cough may be attributed to vagal stimulation by an enlarged spleen. The nervous system was free from abnormal signs, though the selective wasting of the muscle groups of the upper arm was at first suspected as evidence of motor neurone disease. Patchy alopecia has been observed in all admissions, but no undue pigmentation.

The low output of urinary 17-ketosteroids indicates hypogonadism, which is a feature of the disease (Napier, 1951) in man, and in the experimental animal, the Australian marsupial the possum (Bolliger and Backhouse, 1948). The question of amyloidosis was raised because of the extraordinary length of illness and the fact that it is a feature of the disease proved by biopsy in experimentally infected hamsters (Gellhorn, van Dyke, Pyles, and Tupikova, 1946). These animals do not develop hyperglobulinaemia (Stein and Wertheimer, 1942). Sweeney *et al.* (1945) record 20% retention of Congo red at one hour in their case, which, however, also had proteinuria. 17% and 20% retention is strongly suggestive of amyloid disease.

Clearly, infection with *L. donovani* was possible only during the Italian interlude, and reference to the *World-Atlas of Epidemic Diseases* (1952) confirms that the area in which the patient lived for 18 months is one in which the prevalence of visceral leishmaniasis is suspected. It is south of the 10°C. mean annual isotherm, and two *Phlebotomus* species are found there, *P. papatasii* and *P. major*. The accepted vector for *L. donovani* in the western Mediterranean is *P. perniciosus*, which has been identified further north, near Lake Como, and further south, near Pescara, and in Rome and Naples. In the eastern Mediterranean the vector is *P. major*, which has been reported at Ferrara, some 20 miles (32 km.) north of Budrio in the Po Valley. The patient had been nearer the eastern Italian seaboard, 40 miles (64 km.) away, where visceral leishmaniasis is known, on train journeys. A case has been reported (Fusaroli, 1953) at Forli, only 35 miles (56 km.) south-west of Budrio, in a district where it was not previously recognized.

Part of the interest of this case lies in the low total globulin, especially the gamma fraction. Although the formol-gel test is usually positive in kala-azar, it is not a specific test for the disease, but depends on the very high globulin found in the patient's serum. De Vries (1939) has shown that it is positive only when the serum globulin is not less than 3.7 g./100 ml. In the present case the initial globulin level was only 1.7 g./100 ml., and in previous admissions had not exceeded 2.5 g./100 ml. Actual gamma-globulin estimations, by the method of Wolfson, Cohn, Calvary, and Ichiba (1948), were unfortunately not performed until eight weeks after the end of the pentamidine course, giving a result of 0.4 g./100 ml. (normal 0.8–1.2 g.). Serum from a congenital agammaglobulinaemic, from an affected family, gave a result of 0.12 g./100 ml. by this method. During the ensuing four months the gamma-globulin rose to 0.9 g./100 ml.—that is, to within the accepted limits of normal: and at the same time there was some improvement in protein levels, with an unexplained increase in fibrinogen above normal limits. The erythrocyte sedimentation rate (Wintrobe) rose, in spite of an increased packed cell volume.

Cases of kala-azar with a negative formol-gel test fall into two classes: those in which the characteristic protein changes of falling albumin and rising globulin have not yet developed, changes which usually take four or five months; and cases in which such changes never develop. The latter class is held to carry a poor prognosis; Lloyd, Napier, and Paul (1929) found a high relapse rate in this group. The case reported by Chemnitz and Kirsch (1948) had a negative formol-gel throughout two years of illness, during which he had seven courses of anti-leishmanials, and finally died a few weeks after developing herpes zoster: one month before death the total globulin was 1.7 g./100 ml., of which the euglobulin was 0.1 g.

In view of the fluctuation of serum gamma-globulin levels, some just within normal limits, it seems unlikely that this is a case of congenital agammaglobulinaemia; nor is the personal or family history at all suggestive of it. It seems that this is the acquired type, which may be idiopathic or apparently secondary to other conditions, such as disease of the reticulo-endothelial system (Arends, Coonrad, and Rundles, 1954; Zinneman, Hall, and Heller, 1954; Seltzer, Baron, and Toporek, 1955; Good and Mazzitello, 1956), nephrosis leading to hypoproteinaemia, and inadequate protein intake (Krebs, 1946). These cases do not always show an undue proneness to infection (Martin, 1954) or have an absolute absence of gamma-globulin, but it is assumed that an underlying defect in antibody production exists.

Corkill (1949) has suggested that in kala-azar there is a critical point of hypoproteinaemia "below which the body fails to synthesize gamma-globulin in sufficient quantity or kind to meet specific antibody demands, and at such point any factor tending to break down protein or limit its resynthesis would seem thereby to cause activation of a latent infection, or a relapse, or a shortened incubation period." It is possible that in a case of ten years' duration some such balance was present, and permitted only gradual deterioration of the general clinical condition. There seems to be no convincing intercurrent precipitating factor for any of the exacerbations, and the urine did not contain protein before 1957.

It is of course possible that this prolonged mild infection of the reticulo-endothelial system might in some way have affected normal gamma-globulin production. It is harder to conceive of low immune bodies being responsible for an unusually long and symptomless disease.

Summary

A case of kala-azar in an adult Polish male is reported.

Ten years must have elapsed between the patient's leaving an endemic area and the diagnosis of his disease.

The patient was found to have very low serum gamma-globulin, and it is suggested that this might be secondary to the prolonged disease of the reticulo-endothelial system; secondary amyloidosis developed.

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ELECTROPHORETIC DIFFERENTIAL SERUM PROTEIN PATTERN IN KALA-AZAR*

BY

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Ever since Tiselius first introduced the technique of electrophoresis in 1937, much work on protein analysis in various diseases has been undertaken—well summed up by Miller (1955) and Sherlock (1955). Kala-azar, which is widespread in India, has, however, had only a sparse and casual mention in the vast literature on the subject. The *British Medical Journal* (1957) referred to the extensive work of Feinstein and Petersdorf (1956) on the diagnostic importance of gross, moderate, and mild hyperglobulinaemia, but failed to specify kala-azar even though this disease involves a large proportion of the world's population. This failure is not surprising when it is realized that there are only six references to serum protein electrophoretic pattern in kala-azar—namely, those of Cooper *et al.* (1946), Benhamou *et al.* (1949), Le Bourdelles *et al.* (1949), Sen Gupta *et al.* (1953), Agarwal (1957), and Kunwar *et al.* (1957). The work of Cooper *et al.* was based on a study of the sera of one active case and one convalescent case of kala-azar. Benhamou *et al.* also studied two cases, Sen Gupta *et al.* studied the sera of 9 cases, and my colleagues and I (Kunwar *et al.*, 1957) published records of 19 cases.

In addition to hypo-albuminaemia and hypergammaglobulinaemia, Benhamou *et al.* (1949) reported the presence in the sera of his patients of a Factor X fraction with more rapid mobility than the albumin fraction. Other workers, however, failed to confirm the presence of such a fraction. Both Cooper *et al.* and Benhamou *et al.* identified in their cases the presence in strength of a γ-globulin of slower mobility than that of normal γ-globulin. Sen Gupta *et al.* also found this slow-moving γ-globulin in the sera of their 9 cases. This slow-moving fraction, akin to the slow-moving γ_2-globulin found in the sera of rabbits hyperimmunized against type I pneumococci, was held to be characteristic of kala-azar cases and had not been described in other important conditions associated with hyperglobulinaemia. Sen Gupta *et al.* also found a correlation between the complement-fixation test for kala-azar and the presence of this fraction.

Because of sparse and conflicting reports my colleagues and I (Kunwar *et al.*, 1957) considered it worth while to publish a series of 19 cases of kala-azar in which a reassessment of serum was done after the patients had been cured. Our series was larger than any hitherto published, and our findings were at variance in some respects with those of other workers. It would be interesting to compare the findings with those of other workers. I shall attempt to do that.

Our work was based on an analysis of 19 cases with a definite diagnosis of kala-azar. In each case spleen or sternal puncture was positive for Leishman–Donovan bodies. The initial assessment consisted of the clinical picture, Napier's (1921) aldehyde test, and Chopra's (1936) urea-stibamine test; cephalin-cholesterol flocculation, and thymol turbidity tests; estimation of total serum proteins; and paper electrophoretic analysis of serum protein by Durham's hanging strip electrophoretic apparatus, using Whatman No. 3 mm. filter-paper and sodium barbitone buffer at a *p*H of 8.6 (U= 0.075), run for 18 hours at 6 mA. (110 volts). The strips were left in a solution of 0.01% bromophenol blue for 18 hours and were scanned by means of a photovolt scanner. Total and differential white-cell counts were done. An assessment of serum proteins was again made after a full course of urea-stibamine therapy when sternal punctures had become negative for Leishman–Donovan bodies.

Our findings (see Table I) and those of other workers, are given below.

Total Serum Proteins

Our 19 cases showed a hyperproteinaemia (average 7.58 g./100 ml.†) before the start of therapy (Kunwar *et al.*, 1957). Only two cases had an initial total serum protein level of less than 7.4 g./100 ml. Normal averages with the same technique in a separate study (Misra, Shanker, and Bajpai, unpublished) were found to be 7.07 g. It is shown below that this rise in total serum protein occurred in spite of marked hypo-albuminaemia and was mainly due to a rise in γ-globulin. However, Agarwal (1957) failed to elicit any rise in the total serum protein.

Serum Albumin

Hypo-albuminaemia had been reported by Chakravarty *et al.* (1949). All of our cases showed a marked fall in the serum-albumin level (average† 30.14%; range, 20.16%–36.22%). Sen Gupta *et al.* and Agarwal also found a generalized fall of serum albumin, the average value in Agarwal's cases being 25.36%. We found no oedema in spite of hypo-albuminaemia, and the presumptive conclusion is that hypo-albuminaemia is due to hepatic damage.

Alpha-globulins (α_1 and α_2).—These fractions showed only a slight rise of doubtful significance. Normal

*Work on the subject was done at the department of medicine, King George's Medical College, Lucknow, in collaboration with Dr. K. B. Kunwar and Dr. J. S. Bajpai.

†These average figures represent only 14 cases which were followed up.

TABLE I.—*Showing Total and Differential Serum Protein Figures in Kala-azar before and after Treatment*

Case No.	Total Serum Proteins (g.)		Albumin (%)		α_1-Globulin (%)		α_2-Globulin (%)		β-Globulin (%)		γ-Globulin (%)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	7·80	7·30	22·84	28·94	8·93	6·73	10·18	13·42	11·66	15·29	46·39	35·62
2	7·60	7·30	31·32	36·49	10·17	8·99	10·64	10·64	5·39	11·33	42·48	32·55
3	8·80	7·50	22·45	29·27	8·35	8·66	8·96	10·21	7·79	13·25	52·45	38·21
4	7·80	7·60	20·16	28·44	18·42	10·90	11·27	10·84	11·18	14·75	39·17	35·06
5	6·60	6·60	31·56	34·56	5·67	6·33	3·56	10·11	5·00	13·24	54·21	35·76
6	6·00	6·20	31·87	33·34	5·10	6·41	6·19	7·50	8·84	12·69	48·00	40·06
7	7·90	—	30·85	—	2·19	—	5·46	—	22·80	—	38·73	—
8	7·40	—	31·28	—	5·25	—	8·55	—	10·80	—	44·12	—
9	7·80	7·50	30·22	36·20	7·19	6·79	10 22	7·16	10·10	13·95	41·27	35·90
10	7·90	7·40	34·20	39·87	8·22	8·10	8·76	7·25	10·19	12·50	38·63	32·28
11	7·80	—	33·11	—	4·29	—	10·21	—	10·20	—	42·19	—
12	8·00	7·50	36·22	42·90	5·38	6·26	10·66	8·14	10·19	13·67	37·51	29·03
13	8·00	7·60	28·99	35·15	7·30	7·10	9·22	5·19	11·48	14·80	42·09	37·76
14	7·80	—	32·18	—	9·98	—	8·76	—	10·41	—	38·67	—
15	7·70	7·30	30·67	30·69	8·80	9·92	8·27	9·66	10·26	14·25	42·00	35·48
16	7·90	7·80	34·24	40·55	7·62	8·89	9·41	8·27	13·89	14·60	34·24	27·69
17	8·20	7·80	30·90	38·99	8·86	5·85	7·70	10·50	10·12	14·96	42·42	29·90
18	8·00	7·60	28·35	31·75	6·25	6·50	8·01	8·29	12·28	13·16	46·21	40·30
19	7·90	—	31·46	—	5·39	—	8·37	—	10·81	—	43·97	—

average values were 14.01% (Misra *et al.*, unpublished). Using the same technique, we found the average level of 17.72% before treatment and 16.76% after treatment.

Beta-globulin.—Except for one case, this fraction was not raised in any of our cases. Average value before treatment was 8.12% (range 5%–22.8%); normal average, 12.42%. The average figure at the end of therapy was 13.74% (range 11.33%–15.29%). Beta-globulin was definitely raised in only one case—No. 7 (22.8%)—and as in this patient serum cholesterol was also raised the cause may have been the raised lipid content of the blood. Unfortunately this case could not be followed up, and the interesting therapeutic result, if any, on the β-globulin level of serum could not be ascertained.

Gamma-globulins (normal, 23.18%: Misra *et al.*, unpublished).—These were markedly raised in all our cases. Before treatment the average figure in 14 cases was 45.4% (range 39.24%–54.29%). After treatment the average value in these 14 cases was 34.71% (range 27.69%–40.3%). This seems to be the most significant finding in kala-azar cases. Sen Gupta *et al.* (1953) demonstrated that the γ-globulins from the sera of their kala-azar cases showed a mobility significantly slower than normal γ-globulin or even the γ_2-globulin of hyperimmunized serum. Earlier, both Cooper *et al.* and Benhamou *et al.* had reported the presence of slow-moving γ-globulin in their small series. In the cases of Sen Gupta *et al.* the average mobility was 0.4 volt/sq. cm./sec., as compared with normal γ-globulin mobility of 1 volt/sq. cm./sec. at *p*H 8.6 and ionic strength 0.1. In our series no unusual peak was noticed in the electrophoretic pattern after running it for 18 hours.

Total Globulins

There is a definite hyperglobulinaemia in kala-azar. The average value before treatment in our cases was 5.32 g./100 ml., and by the end of treatment it fell to 4.82 g. As already stated, the *British Medical Journal* (1957) drew attention to the findings of Feinstein and Petersdorf (1956), who used the salting-out technique of Cohn and Wolfson (1948), which gives results that closely agree with electrophoretic findings. They conclude that with a gross hyperglobulinaemia of over 5 g./100 ml., there is a one-in-two chance that the patient is suffering from multiple myeloma, sarcoidosis, or collagen disease. In view of our findings kala-azar must be added to the list in this part of the globe, and must be regarded as an important cause of hyperglobulinaemias of over 5 g./100 ml. From our findings it also becomes apparent that, as with multiple myelomas, sarcoidosis, or collagen diseases, the chances of diagnosing kala-azar would become bleak with degrees of hyperglobulinaemia lower than 5 g./100 ml.

Fraction X

As already stated, Benhamou *et al.* detected in the sera of their two kala-azar cases a protein fraction of more rapid mobility than the albumin fraction, and they called this factor "X." They concluded that the presence of Fraction X was of greater value in initial diagnosis and also in assessing the ultimate prognosis of the case. Cooper *et al.*, Sen Gupta *et al.*, and Agarwal failed to detect the presence of any fraction with faster mobility than the albumin fraction. We also could not find any unusual peak in the electrophoretic patterns of our 19 cases.

Correlation with Aldehyde and Chopra's Serological Tests for Kala-azar

Levinson and MacFate (1956) very admirably summed up the diagnostic importance of the aldehyde test thus: "de Vries (1939) stated that a positive formol-gel reaction points to a globulin value of 3.7 g./100 ml. or more . . . it is of diagnostic importance in multiple myeloma (Bauer, 1955), in leishmaniasis (Napier, 1922), in lymphogranuloma inguinale (Benhamou and Gills, 1935), in leprosy (Haseltine, 1924), in endocarditis lenta (Kurten, 1929), and in acute rheumatism (Green *et al.*, 1939)."

Cooper *et al.* (1946) carried out the aldehyde test with separated γ-globulin fraction from the sera of kala-azar patients, but failed to get positive results. They concluded that abnormal γ-globulin could not have represented the whole of the material responsible for the positive reaction with the aldehyde test.

In our series of 19 cases (Kunwar *et al.*, 1957) the aldehyde test was positive in 11 and Chopra's test in 16. Table II shows the correlation between the average protein values and the aldehyde test results as reported by us.

It will be seen that the total serum proteins are the same in the aldehyde-positive and the aldehyde-negative groups, but serum albumin is a little lower and γ-globulin a little higher in the positive group. This is in conformity with the general belief that aldehyde gelation is due to hyperglobulinaemia (Levinson and MacFate, 1956).

Complement-Fixation Test, and Anticomplementary Nature of Sera

Kala-azar serum has also been found to be markedly anticomplementary. Sen Gupta and Adhikari (1952) showed that 16% of aldehyde sera of kala-azar cases

TABLE II

	No.	Total Serum Proteins (Average)	Albumin (Average)	α- and β-Globulins (Average)	γ-Globulin (Average)
Aldehyde-positive ..	11	7·7 g.	28·63%	25·96%	45·41%
,, negative	8	7·7 ,,	32·24%	27·33%	40·43%

were anticomplementary to the extent of about 2 M.H.D. or more. Aldehyde-negative sera of kala-azar cases have rarely been found to be anticomplementary (Sen Gupta *et al.*, 1953). It has been said that the serum changes responsible for positive gelation in the aldehyde test are also responsible in some way for the anti-complementary nature of such sera. It may be noted that a cold precipitable globulin was described in kala-azar serum by Wertheimer and Stein (1944), and a false-positive Wassermann reaction may be obtained in about 10% of cases (Sen Gupta *et al.*, 1953).

In the series of Sen Gupta *et al.*, the complement-fixation test was positive in all the cases, and it was demonstrated that, even when the complement-fixation test alone was positive, there was an increase in slower-moving γ-globulin, associated with decrease of albumin. These authors suggest that the antibody involved in the complement-fixation test for kala-azar is associated chiefly with the slow-moving γ-globulin.

We did not perform the complement-fixation test in our 19 cases.

Thymol Turbidity and Cephalin-cholesterol Flocculation Tests

The biochemical basis of these tests is far from being solved with certainty. But Maclagan (1944), Kunkel and Hoagland (1947), and Martin (1949), have tried to elucidate the part played by γ-globulin in the thymol turbidity reaction; while Hanger (1954) has adequately discussed the role of γ-globulin in the positive cholesterol flocculation test. Thus, although the last word has not been said, the part played by raised γ-globulin is generally agreed upon. Of the 19 cases reported by us (Kunwar *et al.*, 1957), the liver-function tests reveal abnormality in every one. The thymol turbidity reaction varied from 6 to 18 units; cephalin-cholesterol flocculation was ++ in eleven cases and +++ in eight.

Leucocyte Count; Splenomegaly

Total and Differential Leucocyte Count.—Although leucopenia with relative lymphocytosis was found in all the 19 cases, no correlation could be established between the degree of leucopenia or lymphocytosis and the protein fraction abnormality.

Splenomegaly.—No correlation could be established between the size of the spleen and the alterations in the differential serum protein pattern in cases reported by us.

Effect of Therapy

In 14 of our 19 cases, from a laboratory point of view cure was thought to have been attained after a full course of antimony therapy, when sternal smear had become negative for L.D. bodies and when the patient had been relieved of his symptoms. At the end of therapy in these 14 cases there was a slight rise in serum albumin level (the average figure rose from 29.76% to 34.79%), but it was still much below the normal level (50.39%); γ-globulin showed a great fall (on average from 45.40% to 34.71%), but was above the normal average value of 23.18% (Misra *et al.*, unpublished). Total serum protein values also showed a fall (average from 7.58 g./100 ml. to 7.4 g), but was still above the normal value of 7.07 g (controls). These estimations in cases reported by us were done in only 14 cases, as 5 patients had left the hospital prematurely. The changes in total and differential serum protein levels in these 14 cases, before and after therapy, are shown in Table I, which illustrates such changes individually. Unfortunately a complete follow-up of these cases could not be done for practical reasons, but it would have been worth while if we could have followed them up long enough to assess the length of time required for the total and differential serum protein levels to return to normal.

Summary

The literature on total and differential serum protein analysis in kala-azar cases is reviewed, and a comparison is made with results obtained by myself and two colleagues.

Characteristic changes in the serum protein pattern consist of the following. (*a*) Usual rise in total serum proteins. (*b*) Universal and marked fall in serum albumin. (*c*) Gross hyperglobulinaemia of more than 5 g./100 ml. is a characteristic feature. In this respect kala-azar should rank as a major cause of severe hyperglobulinaemia along with multiple myeloma, sarcoidosis, and collagen diseases. (*d*) There is an insignificant rise in alpha- and beta-globulins. (*e*) Aldehyde-positive cases show a higher degree of hyperglobulinaemia than aldehyde-negative cases. (*f*) Literature on slow-moving γ-globulins, and their relationship to the complement-fixation test and aldehyde test, are discussed. (*g*) With treatment, various protein components have a tendency to return to normal. However, biochemical (protein pattern) correction is still incomplete when a clinical and laboratory cure has already been achieved. (*h*) The presence of factor "X" could not be confirmed by most workers.

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BREAST ABSCESS

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The advent of penicillin produced a dramatic change both in the seriousness and in the duration of illnesses due to *Staphylococcus aureus* infections. The problem of hand infections became less serious and puerperal mastitis responded in almost every case to conservative means (Jeffrey, 1947). Hand infections are still amenable to antibiotic therapy, but puerperal mastitis is no longer responding as well as the early results had led us to expect. Early in 1957 several cases of breast abscess which had received antibiotics ran an unduly protracted course. This led us to investigate the material which forms the subject of this paper.

The Investigation

During 1957 we studied 100 consecutive cases of puerperal breast abscess which required surgical treatment. All but two of the patients were delivered in hospital. Ninety-nine breast-fed their babies initially. The single exception was because the baby was transferred to a surgical unit for the treatment of a congenital deformity.

The lactational histories of 200 deliveries occurring in general practice in the area during the same period were reviewed.

Breast-feeding

Duration.—In this area the value of breast-feeding is stressed at the antenatal clinics and during the mother's stay in hospital. Despite this, 20 patients stopped breast-feeding while still in hospital and a further 30 within five days of leaving hospital. Of the two delivered at home, one breast-fed her child for three days and the other for 28 days. Sixty-four patients had given up breast-feeding before the breast became inflamed, and the remaining 36 stopped because of the inflammation. The commonest reasons given for stopping breast feeding in the first group were "cracked nipples" (25 patients) and "failure of lactation" (24 patients). As is shown later, the disease had a much shorter course in those patients who claimed that lactation had failed.

Suppression of Lactation. — Eighty-two patients received stilboestrol in varying dosage. The total dose received appeared to have no relation to the effect on lactation, but we received the impression that a high dosage for a short period is more effective than the same total dose spread over a longer period. We found the dosage ranges commonly advocated were too low to suppress lactation completely when it was established. It was necessary to give 15 mg. of stilboestrol three times a day to suppress lactation in those patients who were still lactating when first seen. Oestrogen-withdrawal bleeding was noticed by 32% of patients who had been taking oestrogen before being seen in hospital, but in none was it severe enough to warrant admission to hospital.

Bacteriology

Sepsis in the Baby.—Infective lesions had been observed in their babies by 46 mothers. Most of these lesions took the form of minor pustules in the skin; but in some cases there were paronychiae, and one baby developed a breast abscess for which it was admitted for in-patient treatment at a children's hospital.

The causative organism was isolated in every case and tested for its sensitivity to penicillin, streptomycin, chloramphenicol, and oxytetracycline. This was done by the method described by Gould and Bowie (1952). In all cases a pure growth of coagulase-positive *Staph. aureus* was obtained. The antibiotic resistance rates are shown in Table I and the sensitivity patterns in Table II.

TABLE I.—*Antibiotic Resistance Rate in 100 Cases of Puerperal Breast Abscess*

Penicillin	93%
Streptomycin	55%
Chloramphenicol	1%
Oxytetracycline	40%
Sterile	1%

TABLE II.—*Antibiotic Sensitivity Patterns in 100 Cases*

Penicillin	Streptomycin	Chloramphenicol	Oxytetracycline	No.
Sensitive	Sensitive	Sensitive	Sensitive	7
Resistant	,,	,,	,,	37
,,	Resistant	,,	,,	14
,,	,,	Resistant	,,	1
,,	,,	Sensitive	Resistant	39
,,	Sensitive	,,	,,	1
	Sterile			1

Duration of Illness

The duration of the illness was calculated from the first day on which pain was felt in the breast until the incision had healed. This varied from 14 to 148 days, with an average of 50 days. These details, together with the corresponding ones for the periods between onset and the incision, and the incision and healing, are shown in Table III. As most cases were incised on the day they were first seen, the average interval between the onset and the incision corresponds closely with the average time which elapsed before the patients were referred for hospital treatment. In 24 cases in which breast-feeding was stopped because of failure of lactation the average time between the onset of symptoms and the first incision was the same as that of the whole series—that is, 15 days—but the time from incision until healing occurred was only 19 days.

TABLE III.—*Duration of Disease*

	In Whole Series		In 24 Cases with Failure of Lactation	
	Range	Average	Range	Average
No. of days from onset until incision	4–134	15	5–42	15
No. of days from incision until healing	4–103	35	4–63	19
No. of days from onset until healing	14–148	50	14–71	34

TABLE IV.—*Antibiotic Treatment*

Antibiotic	No. of Patients	Days of Treatment	
		Range	Average
Penicillin	86	1–17	6·5
Streptomycin	8	5–15	8·0
Chloramphenicol	8	5–15	8·0
Oxytetracycline	11	4–25	6·0
Chlortetracycline	3	4–8	6·3

Recurrence of Abscesses.—A further abscess developed in the same breast in 24 patients and in the opposite breast in 10. In retrospect it appeared that these abscesses were associated with the recurrence of

lactation in patients in whom lactation appeared to be so satisfactorily suppressed when they were first seen that they were given no further stilboestrol.

Treatment

The antibiotics used and the average duration of treatment are shown in Table IV. The interval between the onset of symptoms and the start of antibiotic therapy varied from one to 17 days, with an average for the series of three days.

In every case antibiotics were stopped when the diagnosis of a breast abscess was made. Stilboestrol, in a dosage of 45 mg. daily in divided doses, was given if milk could be expressed from the breasts.

The breast was incised as soon as the presence of pus was diagnosed. In the exceptional doubtful case the diagnosis was confirmed by aspiration with a wide-bore needle. A soft rubber drain was inserted and left in position for 24–48 hours; thereafter the cavity was lightly packed with gauze soaked in eusol.

In the later cases we used a circumferential incision of the skin as advocated by Haagensen (1956) for the excision of simple tumours. Dissection in the mammary tissue itself was in the line of the ducts. These incisions proved adequate for drainage and post-operative treatment and healed with a better cosmetic result than the more conventional radial incision.

Discussion

Breast abscess appears to be a more protracted disease than in pre-antibiotic days, when the lesion healed in three to four weeks (Macpherson, 1943).

When the organism is resistant to the antibiotic used the pathological features are modified unfavourably. Tissue necrosis and pus formation are retarded, while repair proceeds uninhibited. A thick fibrous wall forms around the abscess. This delays resolution and prevents the cavity collapsing after incision. In extreme cases the abscess is rendered quiescent and the residual mass resembles a carcinoma (Rose, 1956). A further result of this increased fibrosis is the tendency to produce unsightly shrunken breasts.

Another clinical variety is a diffuse oedematous inflammation of the breast which persists for many days before any localization or pus formation becomes apparent. Continuation of antibiotic therapy did not seem to help in this type of lesion, and more satisfactory results were obtained by withholding further antibiotics and applying local heat.

From a review of hospital records in Edinburgh it is estimated that in 1957 between 3 and 4% of all women delivered developed breast abscesses requiring hospital treatment.

To estimate the proportion of puerperal breast infections which resolve without hospital treatment the post-natal histories of 200 consecutive deliveries which occurred in the General Practice Teaching Unit of Edinburgh University were studied. Of these, 35% were delivered at home (Table V). Only one case in four which developed mastitis progressed to abscess formation. The incidence of the latter was the same as that calculated for the whole region.

TABLE V.—*Incidence of Mastitis and Breast Abscess in 200 Consecutive Deliveries*

	No.	Breast Infections		Breast Abscess	
		No.	%	No.	%
Home confinements ..	70	5	7·1	2	2·8
Hospital ,, ..	130	20	15·4	4	3·1
Total	200	25	12·5	6	3·0

The incidence of breast infections following hospital deliveries was more than double that following home confinements (Table V). This was associated with the heavy colonization of the baby's nasopharynx with organisms from the environment in which it spends the first few days of life.

These organisms were the same as those recovered from the breast abscesses but were different from those carried in the mother's nares.

An important aetiological factor in breast infections is engorgement with milk. This commonly results from the stopping of breast-feeding without adequate measures being taken to suppress lactation and empty the breasts. At least one-third of our patients had stopped breast-feeding because they were opposed to it. They had breast-fed their babies reluctantly while in the maternity hospital, but gave up as soon as they left. Few sought medical advice about suppressing lactation.

These findings suggest that breast-feeding should not be forced on unwilling mothers. These patients would benefit more from proper instruction in bottle-feeding while in hospital.

When engorgement has occurred it is probably best managed by gentle manual expression of the milk, as described by Waller (1946). Breast pumps or the "humalactor" may be used if available (Ratcliff, 1951). Engorgement occurring during lactation usually responds to a short course of oestrogen combined with manual expression.

Continued lactation without engorgement may delay healing. As shown in Table IV, the healing-time in cases where lactation failed was shorter than in the series as a whole.

Successful conservative treatment includes the use of an antibiotic to which the organisms are sensitive. Until the sensitivity of the causative organism has been determined it should be assumed that it is the same as that of the environmental organisms of the maternity unit concerned. In this region chloramphenicol was the drug of choice. In the series from the General Practitioner Teaching Unit 10 of the 11 cases treated with chloramphenicol responded satisfactorily (Table VI).

TABLE VI.—*Antibiotic Treatment of Puerperal Mastitis*

Antibiotic	No. Treated	No. Recovering
Penicillin	10	5
Chloramphenicol	11	10
Erythromycin	1	1
Penicillin and streptomycin ..	2	2
None	1	1
Total	25	19

We have estimated that the cost per patient of drugs, dressings, and nursing services was over £10, although all were treated as out-patients.

Conclusion

From these observations we feel justified in making the following recommendations. (1) Every measure should be taken to prevent colonization of the baby by antibiotic-resistant staphylococci. (2) Mothers who

remain opposed to breast-feeding despite full propaganda should be allowed to bottle-feed their babies and receive instruction in the correct technique for doing this. (3) If breast-feeding is stopped, lactation should be vigorously suppressed under medical supervision. We would suggest that stilboestrol be given in a dosage of 45 mg. three times a day. The breast should be emptied regularly by manual expression and lumpy collections dispersed by gentle centripetal massage. (4) An antibiotic should be given if infection is suspected. If there is no local response after 48 hours the antibiotic should be stopped. Prolonging antibiotic treatment in the absence of a response leads to excessive fibrosis and protraction of the disease. (5) The antibiotic of choice in this series was chloramphenicol.

Summary

One hundred consecutive cases of puerperal breast abscess requiring hospital treatment were studied. It was shown that the duration of the disease has increased compared with earlier reports from the same hospital (Macpherson, 1943). This increase seems to be due to the widespread use of antibiotics.

Very high resistance rates to antibiotics were shown. The failure of antibiotic treatment was largely due to this resistance.

The modification of the pathology of the disease when treated with antibiotics to which the organism is not fully sensitive is discussed.

The importance of adequate suppression of lactation and of avoidance of breast engorgement in the prevention of infection in those who stop breast-feeding is stressed.

Recommendations to reduce the incidence and duration of the disease are made.

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Medical Memoranda

Xanthocillin Cream for Local Treatment

The type of dermatological case for which local antibacterial treatment is required has altered considerably in recent years. Impetigo contagiosa and other relatively straightforward superficial infections of the skin are now quite uncommon in the hospital clinic. The eczematous eruptions and cheiropompholyx with gross pyogenic secondary infection often combine lymphangitis, cellulitis, lymphadenopathy, and some degree of systemic disturbance, and in these cases a systemic antibiotic is usually indicated; local treatment then aims at drainage of pus and anti-eczematous rather than antibacterial measures.

There remains a third group of very difficult conditions comprising some types of seborrhoeic dermatitis, particularly those with a tendency to flexural distribution, to weeping, and to superficial folliculitis; intertrigo, particularly with weeping and the development of fissures in the flexures; and varicose (stasis) dermatitis in which infection often plays an important though not the primary part. The role of bacterial infection in these disorders is difficult to assess, but antibacterial applications often produce striking improvement. Indeed, it is in this type of case that local antibiotic treatment is most used at the present time.

Cultures made from the affected surfaces yield pathogens the antibiotic sensitivities of which can be determined. The application of the appropriate antibiotic will frequently be followed by improvement, but all too often the condition relapses after a week or two. Further cultures now reveal a fresh pathogen, this time resistant to the antibiotic which has been used. Because of this the choice of antibiotic according to the results of cultures does not always give the best therapeutic results although it seems logical. Indeed, the use of the "wrong" antibiotic sometimes gives better clinical results than the "right" one.

It is common for these eruptions to become very much worse when a new treatment is applied. This aggravation is sometimes due to allergic hypersensitivity to a fresh antibiotic, but more often it appears to be a non-specific intolerance which at another time, in the same patient, would not occur. This unpredictable non-specific intolerance of treatment makes the management of these cases so much the more difficult.

A clinical trial of a new antibiotic cream therefore presents considerable difficulties. The cream has to be used chiefly in cases of the third group, mentioned above, where the therapeutic results are seldom immediate or clear-cut. Individual cases vary a great deal and may be difficult to classify, so that the selection of cases for treatment is difficult and the arrangement of controls even more so. Presumably, in order to overcome the difficulty of repeated superinfection, the antibiotic should have as wide a range of action as possible with the least tendency to allow the development of resistant strains. It should also have a low sensitizing index—a property which can be expected to emerge only after use in a considerable number of cases; the likelihood of sensitizing 1 to 2% of patients treated would be a serious drawback, and it may be necessary to treat 100 to 200 people before this can be appreciated.

XANTHOCILLIN

Xanthocillin is an antibiotic derived from *Penicillium notatum* (Rothe, 1954) and has been isolated in the form of yellow crystals which contain two components, x and y, in the proportion of about 4:1. The chemical properties of the two components are very similar: they are sparingly soluble in water, alcohol, ether, and other common solvents, and stable in normal conditions.

Rothe reported that xanthocillin was not suitable for systemic therapy because of its toxic properties and poor absorption, and so its use is limited to topical application. *In vitro* tests have shown that most of the common Gram-positive and Gram-negative pathogens, including *Proteus* and *Pseudomonas pyocyanea*, are sensitive to xanthocillin, and there is also some suppressive action against *Mycobacterium*

tuberculosis and certain pathogenic fungi and yeasts. Bacterial resistance to the antibiotic develops very slowly and no cross-resistance with other antibiotics has been reported. The sensitizing power of xanthocillin is said to be low.

The present trial with xanthocillin cream was carried out over a period of some months on a group of in-patients with a variety of eczematous and intertriginous eruptions, in all of which bacterial infection was thought to be playing a part. Most of these patients had already been treated with other antibiotics or with antiseptic applications; in some cases the eruption was symmetrical and permitted simultaneous comparison to be made between xanthocillin and other methods in routine use; these included iodochlorhydroxyquinoline, neomycin, and various other antibiotics.

At the same time xanthocillin cream was applied in the form of patch tests for 48 hours to the normal skin of 20 other subjects.

RESULTS

The patch tests carried out on normal skin were all negative and thus failed to show any primary irritant or toxic property in the cream.

When applied to the inflamed and eczematous skin there was no case in which aggravation of the eruption appeared to result. This in itself is encouraging, for the patients being treated were those in whom non-specific aggravation from treatment is rather often seen.

As to the therapeutic efficiency of the cream it is not possible to give more than a clinical impression. There were some cases in which the cream was of no apparent benefit; there were some in which rapid and striking improvement was produced after other antibiotics had failed. Generally speaking, the impression was that xanthocillin cream produced results which were on a par with other treatments with which it could be compared.

One may sum up these results by saying that xanthocillin did not show irritant or other objectionable properties and that these preliminary results warrant a more extensive trial. If the antibiotic action which has been demonstrated *in vitro* is exerted also on the surface of the skin, xanthocillin cream should prove to be a very useful local application in suitable cases.

I am indebted to Dr. C. N. Brown, of the Distillers Company, for supplies of xanthocillin cream and for information regarding xanthocillin.

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REFERENCE

Rothe, W. (1954). *Dtsch. med. Wschr.*, **79**, 1080.

Preliminary Communications

The Physiopathology of Acute Haemolytic Shock

This paper summarizes the results and conclusions derived from the observation of a number of cases of transfusion reaction in patients, and from about 1,000 experiments on animals and on ourselves.

Distilled water was injected intravenously into dogs (5 to 10 ml./kg. body weight) and into ourselves and patients suffering from anaemia (100 to 150 ml.), in all cases with no detectable effects. Intravenous reinjection of our own haemolysed blood (100 to 130 ml.) and haemolysed autotransfusion into dogs (2 ml./kg.) also had no detectable effect. Haemolysed blood of group O also can be safely injected into recipients of any other group.

Haemolysed blood of group A can be transfused into individuals of any other blood group, provided it is freed from its stroma; in experiments in dogs no haemolytic shock was found to occur after the transfusion of heterospecific blood, if this had been previously freed of stroma. Stroma itself, on the other hand, does produce shock. Experiments on ourselves showed that the injection of blood of a different group, containing stroma, causes haemolytic shock, while the same blood freed of stroma has no effect.

We consider haemolytic shock to be closely related to anaphylactic shock. Our investigations in this connexion gave the following results:—In both we observed the same serological effects: diminution of complement, of haemolysins, of agglutinin titre, and of bactericidal properties. The haematological effects were also identical: primary leucopenia followed by leucocytosis, granulocytopenia followed by granulocytosis, lowered sedimentation rate of the red corpuscles, lowered Sabrarés index, polycythaemia, eosinopenia, thrombocytopenia, and disturbance of coagulation. The biochemical changes, too, were the same: alteration of the refractive index, lowering of the polarographic wave, increase of the serum potassium level, fall in calcium level and alkali reserve, and diminished intestinal absorption of glucose. In some of the experiments hyperglycaemia was noted, and a fall in the cholinesterase level.

One attack of haemolytic shock affords protection against a subsequent one, and prophylactic histamine treatment has a similar effect. Physostigmine, on the other hand, aggravates the shock.

The consequences of haemolytic shock are the same as those of the anaphylactic variety: biliary obstruction, contraction of the peripheral capillaries, and an increase of lymph flow in the thoracic duct. The muscle fatigue which Eppinger observed in histamine shock is also to be seen in haemolytic shock.

The simultaneous injection into the carotid sinus of blood from another person and of the recipient's own plasma produces shock.

We are able to bring about conditioned reflexes in haemolytic shock as well as in histamine shock. In the former, both the pressor and the depressor reflexes are diminished. The heart damage observed is not the result solely of disturbance of the peripheral circulation, but also occurs in Starling's heart–lung preparation, even when an adequate venous in-flow has been ensured.

Drugs effective in anaphylactic shock (antazoline, calcium, procaine, nicotinamide, chlorpromazine) also alleviate haemolytic shock.

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Reviews

MEMOIRS OF FELLOWS OF THE ROYAL SOCIETY

Biographical Memoirs of Fellows of the Royal Society. Volume 3, 1957. A new series in continuation of *Obituary Notices of Fellows of the Royal Society*, Volumes 1–9 (1932–1954). (Pp. 328; illustrated. 30s.) London: The Royal Society. 1957.

The first Fellow to be commemorated in this book is Alexander, Earl of Athlone (1874–1957). Sir Charles Dodds points out that, in addition to a distinguished record as soldier, statesman, Governor-General of South Africa and of Canada, and Chancellor of London University, Lord Athlone rendered conspicuous services to undergraduate and postgraduate medical education, to hospitals, to public health, and to the organization and welfare of the nursing profession.

There are memoirs of four Fellows who are illustrious in medical science. Professor J. Craigie tells of the work of Arthur Felix (1887–1956), the discoverer with Edmund Weil of the diagnostic test in typhus fever known as the Weil–Felix reaction, which led Felix to the discovery of the H and O antigens of organisms of the *Proteus* and enteric groups, the Vi antigen in virulent strains of the typhoid bacillus, the epidemiologically important method of typhoid phage typing, and its international standardization. Sir Henry Dale writes of the valuable research work which Sir Percival Hartley (1881–1957) accomplished, especially in the service of the Medical Research Council for the establishment, both national and international, of a uniform series of biological standards. Hartley formed one of the important links between the Council and the Ministry of Health. As Sir Henry notes, it was the work of Hartley and his collaborators on diphtheria immunization which fortified officials of the Ministry of Health in launching the campaign for antidiphtheria inoculation of the nation's children. One of the greatest threats to child life has thus been reduced almost to insignificance. It should be observed that in 1945 Hartley also did research work on the standardization and potency of penicillin (*vide* bibliography).

Sir Samuel Bedson has written an admirable and sympathetic account of H. M. Turnbull, one of the greatest morbid anatomists and pathologists of all time. Alas! he was also to some extent the mute, though not inglorious, Milton of pathology. Treasures of knowledge and of experience were stored in Turnbull's brain. In the course of conversation he would impart some of them to his colleagues and pupils, but much of the knowledge he might have given to the world died with him, for he always aimed at an ideal perfection before putting pen to paper. Bedson has ably recorded the publications and work of this reluctant writer and speaker, but most of them only appeared under pressure from his collaborators, to whom he was ever generous. Dr. J. H. Gaddum contributes an interesting memoir of J. W. Trevan (1887–1956), whose researches in pharmacology, first in the Wellcome Physiological Laboratories and subsequently as director of the laboratories and Research Director of the Wellcome Foundation, so greatly advanced knowledge of the subject.

The other 16 memoirs of scientific Fellows are equally interesting and informative. Among them may be mentioned the able description of the work and lovable character of F. G. Donnan, the chemist; the tribute paid to F. Soddy, a pioneer of research into atomic disintegration and the coiner of the term "isotopes"; and the account of my former teacher, J. S. E. Townsend, of Oxford, who is rightly termed by A. von Engel "one of the great physicists of this century."

This third volume of the new series of *Memoirs of Fellows of the Royal Society* worthily upholds the high reputation of the preceding volumes, and the value of this series to the history of science and to the scientific world generally must once more be emphasized.

ARTHUR S. MACNALTY.

THE AGEING ORGANISM

Ciba Foundation Colloquia on Ageing. Volume 4. *Water and Electrolyte Metabolism in Relation to Age and Sex.* Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Maeve O'Connor, B.A. (Pp. 327+xii; illustrated. 45s.) London: J. and A. Churchill, Ltd. 1958.

This is the fourth volume in the Ciba Foundation series of colloquia on ageing. Despite the considerable advance in understanding of the physiology of fluid and electrolyte balance that has accrued as a result of the researches of the past twenty years, many problems relating to the distribution of the body fluids and to the mechanisms whereby these fluids are regulated, both in amount and composition, remain unsolved. The chief purpose of the contributors to the present volume was to discuss various aspects of these problems in relation to age and sex.

Interested paediatricians are aware that the fluid compartments of the infant bear different relationships to one another, as well as to total body water and to body mass, as compared with those of the adult. There are excellent chapters on this subject and on the capacity of the infant kidney to deal with loads of fluid and electrolyte. The inadequacy of the infant's total body water in relation to metabolic needs, and the relative failure of the kidney to preserve the body economy when stressed, are well described. Whether these differences between infants and adults can be ascribed to differences in hormonal influences is difficult to determine.

Less work has been done on the renal function of the ageing organism. It is, however, apparent that the older subject is unable to readjust equilibrium with the facility of the young subject. There are interesting contributions on maintained abnormal steady states, on renal function in cardiac and respiratory failure, and on magnesium depletion.

Apart from pointing the present state of research into these problems, the chief subsidiary value of this volume is in the formulation of the important questions awaiting investigation, and in the insight which those newly interested in this field can obtain into the study methods being used.

R. A. WOMERSLEY.

DIAGNOSTIC DIFFICULTIES

Difficult Diagnosis. A Guide to the Interpretation of Obscure Illness. By H. J. Roberts, M.D. (Pp. 913+xi. £6 13s.) London and Philadelphia: W. B. Saunders Company. 1958.

This is an odd but by no means negligible book. It is a book in which a consultant does what so many of his fellows have dreamed of doing and garners the fruit of his experience for the benefit of others. This is a task that becomes progressively less rewarding as we

move through the second half of the twentieth century, because experience is personal and much of medicine has changed in our lifetime from art to technology. Part I, which has the title "Groupings of Related Diseases Frequently Producing Puzzling Illness," extends to 560 pages and includes an atlas of skin disorders in the last 45 pages. Some idea of the quality and content of this first part may be given by the following quotation from the section on hepatic coma in the chapter entitled "Hepatic Disease and Jaundice."

> "It is vitally important that Wernicke's encephalopathy not be misdiagnosed as hepatic coma, due to the salutary effects of large doses of thiamine in the former state.[142 355] The importance of not overlooking hepatic hypoglycemia (p. 21) and magnesium deficiency (p. 67) as causes of bizarre mental behaviour, neurologic phenomena, and coma have been discussed previously.[61 241] Although the so-called 'flapping tremor' was at one time thought to be characteristic of hepatic failure, it has also been observed in pulmonary insufficiency,[1112] renal failure, polycythemia vera, severe malnutrition, and steatorrhea.[356] Two other important and potentially treatable conditions that must be considered in the alcoholic patient with cirrhosis who develops serious neurologic involvement are a subdural haematoma and an infectious meningitis.[142d]"

A large part of the book, but not all of it, is as good as this. Part I is followed by 100 closely printed pages of references, about 2,500 of them. Part II is a classification and analysis of useful diagnostic procedures; it comprises nearly 200 pages. Finally, there are a 25-page index of signs, symptoms, and laboratory manifestations, and a general index of nearly 40 pages. I should regard Dr. Roberts's book as an extravagance to buy—it costs £6 13s.—but I should be happy to have it on my shelves to consult when I am thinking over a puzzling case or preparing for a clinical demonstration.

L. J. WITTS.

ELECTROLYTE CHANGES IN SURGERY

Electrolyte Changes in Surgery. By Kathleen E. Roberts, M.D., Parker Vanamee, M.D., and J. William Poppell, M.D. (Pp. 113+x; illustrated. 34s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

This book, though comparable in size, is very different in style and emphasis from the well-known books by LeQuesne and by Wilkinson on the same subject. For example, in this book only six pages are given to post-operative changes in water and electrolytes, whereas the discussion of acid–base alterations runs to 49 pages. We have here, in effect, a good account of those matters which have interested and engaged the authors, rather than a comprehensive survey of the field suggested by the title. The emphasis throughout is biochemical, and there is a note almost of despair on page 37, when it is admitted that "the diagnosis of the late stage of respiratory alkalosis is difficult to make except by history and physical findings."

This is a book for those already interested in electrolyte metabolism rather than for the general reader. In addition to the central section on acid–base troubles, it provides useful insights into the dangers of excessive transfusion and pre-operative purgation. There is no index, but the table of contents is adequate.

D. A. K. BLACK.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Der Erythrocyt. By Lothar Friederici, M.D. With a foreword by Prof. Dr. R. Duesberg. (Pp. 204+viii; illustrated. DM. 24.) Heidelberg: Dr. Alfred Hüthig Verlag. 1959.

Klinik, Pathologie und Probleme der Periarteriitis Nodosa des Nervensystems. By Albrecht Stammler, M.D. (Pp. 153; illustrated. DM. 18.) Heidelberg: Dr. Alfred Hüthig Verlag. 1959.

Mental Illness in London. By Vera Norris, M.B., Ph.D. (Pp. 317. 35s.) London: Chapman and Hall, for the Institute of Psychiatry. 1959.

Bilharziasis of the Ovary in Egypt. By M. Alaedine Shafeek, M.B., B.S., D.G.O. (Pp. 48+xi; illustrated.) Cairo: Sirovic Bookshop. 1958.

British Instruments. Directory and Buyers' Guide 1959. (Pp. 322; illustrated. 42s.) London: Scientific Instruments Manufacturers Association and United Science Press Limited. 1959.

The Mast Cells. By James F. Riley, M.B., Ch.B.(Hons.), M.D., Ph.D., D.M.R.T., F.R.C.S.E. Foreword by Sir Henry Dale, O.M., G.B.E., F.R.C.P., F.R.S. (Pp. 182+x; illustrated. 30s.) Edinburgh and London: E. and S. Livingstone Ltd. 1959.

Readings in Psychoanalytic Psychology. Edited by Morton Levitt, Ph.D. With 24 contributing authors. (Pp. 413+xiv. $8.50.) New York: Appleton-Century-Crofts, Inc. 1959.

Curare and Curare-like Agents. Edited by D. Bovet, F. Bovet-Nitti, and G. B. Marini-Bettòlo. (Pp. 478+xi; illustrated. 85s.) Amsterdam: Elsevier Publishing Company. London: D. Van Nostrand Company Ltd. 1959.

Medicina Interna de Urgencia y de Cuadros Agudos. By Egidio S. Mazzei and M. Leticia Diaz Soto de Mazzei. Second edition. (Pp. 959+xiv; illustrated.) Buenos Aires: Lopez and Etchegoyen, S.R.L. 1958.

Sex, Love and Society. By E. R. Matthews, M.R.C.S., L.R.C.P. (Pp. 199. 12s. 6d.) London: Victor Gollancz Ltd. 1959.

Bigger's Handbook of Bacteriology for Students and Practitioners of Medicine. Seventh edition by F. S. Stewart, M.D. (Dublin), F.R.C.P.I. (Pp. 611+x; illustrated. 37s. 6d.) London: Baillière, Tindall and Cox. 1959.

Le Choléra. La Première Épidémie du XIX^e Siècle. By Louis Chevalier. (Pp. 188+xvii; illustrated. 750 fr.) La Roche-sur-Yon: Imprimerie Centrale de l'Ouest. 1958.

History of the Second World War. United Kingdom Medical Series. The Army Medical Services. Campaigns. Volume III. ***Sicily, Italy, Greece. (1944-45.)*** By F. A. E. Crew, F.R.S. (Pp. 645+xxxviii; illustrated. £5.) London: Her Majesty's Stationery Office. 1959.

Shakespeare and Medicine. By R. R. Simpson, M.B., Ch.B., F.R.C.S., F.R.C.S.Ed. (Pp. 267+vi. 25s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1959.

The Sixth Sense. An Inquiry into Extra-Sensory Perception. By Rosalind Heywood. (Pp. 224. 21s.) London: Chatto and Windus. 1959.

Modern Trends in Pathology. Edited by Douglas H. Collins, O.B.E., M.D.(L'pool), F.R.C.P.(Lond.). (Pp. 334+x+12; illustrated. 70s.) London: Butterworth and Co. (Publishers) Ltd. 1959.

Group Processes. Transactions of the Fourth Conference October 13, 14, 15, and 16, 1957, Princeton, N.J. Edited by Bertram Schaffner, M.D. (Pp. 266. $4.50.) New York: Josiah Macy Jr. Foundation. 1959.

A Psychological Study of Typography. By Sir Cyril Burt. With an introduction by Stanley Morison. (Pp. 68+xix. 15s.) London: Cambridge University Press. 1959.

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ACROPARAESTHESIA AND THE CARPAL TUNNEL

One of the commonest types of patient seen in a neurological clinic is a woman between 40 and 60 years of age who wakes up several times each night with painful paraesthesiae in the fingers and pain in the forearms and sometimes as high as the shoulder. In addition to the paraesthesiae the fingers usually feel stiff and sometimes swollen, and finger movements are clumsy and difficult. The symptoms, which are often bilateral, are usually worse during the night after specially heavy housework or a washing day. Similar symptoms may occur during the day, but the nocturnal ones are more severe. This condition was given the name of acroparaesthesia by F. Schultze[1] in 1893, and over the years various unconvincing explanations were given for it. In 1945, however, S. Behrman[2] suggested that it was essentially mechanical in origin and was due to a minor degree of compression of the brachial plexus. In the same year F. M. R. Walshe[3] attributed the condition to traction and compression of the first rib on the lower components of the brachial plexus and sometimes also on the subclavian artery; this was brought about by drooping of the shoulder girdles resulting from hypotonia of the shoulder muscles. Many of the patients afflicted by the disorder improved with shoulder-girdle exercises—a fact which seemed to favour Walshe's explanation. In 1949 M. J. F. McArdle[4] suggested that the cause of acroparaesthesia was compression of the median nerve in the carpal tunnel rather than a compression of the brachial plexus by the first rib. Prior to this, in 1947, W. Russell Brain, A. Dickson Wright, and M. Wilkinson[5] had shown the importance of compression of the nerve in the carpal tunnel in causing a progressive median-nerve lesion, but McArdle was the first to propose that the commoner syndrome of acroparaesthesia with little in the way of abnormal physical signs might be due to a similar mechanism. Acting on this suggestion, M. Kremer and his colleagues[6] divided the volar retinaculum in 40 patients suffering from acroparaesthesia, and in 37 there was immediate and permanent relief of symptoms. In two patients who were not benefited it was found at a second operation that the distal fibres of the retinaculum had not been divided; and on division of these the symptoms were relieved. In the remaining patient a cyst arising from the flexor tendons and compressing the median nerve was found.

Compression of the median nerve in the carpal tunnel has been confirmed as a cause of acroparaesthesia by H. Garland and his colleagues[7] and by K. W. G. Heathfield.[8] When a careful history is taken it is usually clear that the area affected by the paraesthesiae is within the distribution of the median nerve, with escape of the little finger, though some patients have great difficulty in describing exactly where they feel the pain. Physical signs of median-nerve dysfunction may be absent, but in some patients there is slight wasting, sometimes more easily felt than seen, on the outer side of the thenar eminence and slight sensory impairment on the palmar aspect of the index and middle fingers. The disorder may be associated with a local lesion at the wrist such as tenosynovitis of the flexor tendons, rheumatoid arthritis, a malunited fracture of the scaphoid, or a Colles's fracture in which there is some encroachment on the carpal tunnel. It may also occur in generalized diseases such as acromegaly[9] or myxoedema,[10] in which there may be a reduction in size of the carpal tunnel, and it is also seen in pregnancy and occasionally seems to be familial in that two or three siblings may be affected.[11] In the majority of cases, however, there is no obvious local factor, the condition being most common in women who have much housework to do and only occasionally occurring in men. Operative division of the volar retinaculum is curative, but is needed only in some patients, since many obtain complete relief of the nocturnal paraesthesiae by putting a light plaster splint on the wrist when they go to bed.

Among the questions which remain are why many patients can be helped by shoulder-girdle exercises and why some have pain in the forearm and even in the upper arm. If the arterial supply is obstructed by a sphygmomanometer on the upper arm of a patient with compression of the median nerve the symptoms of acroparaesthesia are usually quickly produced and sensory impairment in median-nerve

[1] Schultze, F., *Dtsch. Z. Nervenheilk.*, 1893, **3**, 300.
[2] Behrman, S., *Proc. roy. Soc. Med.*, 1944–5, **38**, 600.
[3] Walshe, F. M. R., *Brit. med. J.*, 1945, **2**, 596.
[4] McArdle, M. J. F., Oral communication at Association of British Neurologists, 1949.
[5] Brain, W. R., Wright, A. D., and Wilkinson, M., *Lancet*, 1947, **1**, 277.
[6] Kremer, M., Gilliatt, R. W., Golding, J. S. R., and Wilson, T. G., ibid., 1953, **2**, 590.
[7] Garland, H., Bradshaw, J. P. P., and Clark, J. M. P., *Brit. med. J.*, 1957, **1**, 730.
[8] Heathfield, K. W. G., *Lancet*, 1957, **2**, 663.
[9] Kellgren, J. H., Ball, J., and Tutton, G. K., *Quart. J. Med.*, 1952, **21**, 405.
[10] Murray, I. P. C., and Simpson, J. A., *Lancet*, 1958, **1**, 1360.
[11] Turner, J. W. A., Heathfield, K. W. G., and Taylor, G. W., in *British Surgical Practice—Surgical Progress*, 1958, London.
[12] Russell, W. R., *Med. Press*, 1958, **240**, 1151.

distribution may occur, which suggests that ischaemia higher in the arm may aggravate the median-nerve ischaemia caused by compression in the carpal tunnel. As Walshe suggested, when there is drooping of the shoulder girdles there may be some degree of obstruction of the subclavian arteries. If this drooping of the shoulder girdle can be corrected by exercises the subclavian compression should be overcome, with subsequent improvement in the symptoms. The reason for the pain in the forearm and sometimes the upper arm is uncertain, but there is no doubt that it is usually relieved by operative division of the volar retinaculum and quite often by a splint on the wrist at night.

Paraesthesiae in the fingers can occur in polyneuritis or in diseases of the spinal cord such as disseminated sclerosis or subacute combined degeneration of the cord, but in these disorders they are usually present by day as well as by night and are accompanied by abnormal physical signs. Difficulties in diagnosis may, however, arise with protrusion of cervical disks and with cervical spondylosis. Paraesthesiae in the fingers are common with a lateral disk protrusion compressing an emerging nerve root, but in the early stages there are often pain and stiffness of the neck, aggravation of the pain by certain movements of the neck, and impairment of one or more of the arm jerks. In cervical spondylosis, with encroachment by osteophytes on the intervertebral foramina and fibrosis of the root sleeves, pain in the arms and paraesthesiae in the fingers may also occur, and in such cases the diagnosis from acroparaesthesia due to a median nerve compression may be difficult and the therapeutic test of a night splint may be very helpful.

W. Ritchie Russell[12] in a recent article takes a rather different point of view, suggesting that too much attention has been given to looking for a pathological abnormality at one level only. He thinks that whatever the primary cause the whole length of the peripheral nerves in the arms is involved and that the fibrous sheaths and compartments of the nerves become inflamed and inelastic, the process being aggravated by normal movements of the arms. This seems to be a return to the old concept of brachial neuritis, and the main evidence he adduces in support of it is his frequent finding of tenderness apparently over the nerve trunks. The fact that so many of the patients are relieved by a splint at night or by decompression of the median nerve in the carpal tunnel makes this concept rather improbable. Alternatively, if Ritchie Russell's hypothesis is correct, then breaking the vicious circle at the appropriate point—the carpal tunnel—relieves the symptoms and puts a stop to the spread of the pathological process.

SYNDROMES OF ISLET-CELL TUMOURS OF THE PANCREAS

Although uncommon, the syndrome associated with insulin-secreting tumours of the pancreas is well known. The symptoms arise from the excessive production of insulin, with resulting hypoglycaemia, and they fall into predictable patterns. The hypoglycaemic episodes occur before breakfast or at other times several hours after a meal. They are often brought on by physical exertion, and include hunger, pallor, sweating, tachycardia, and nausea. These may be followed by loss of consciousness, which may be brief and resemble a simple faint or be more severe, with epileptic convulsions and various neurological signs; occasionally a severe hypoglycaemic episode is fatal. Disturbances of behaviour are common so that the patient may be regarded as drunk or, when they persist, be referred to a psychiatrist. The blood sugar is always abnormally low when symptoms develop. If necessary, the diagnosis can be confirmed by having the patient fast for 24 hours while serial determinations of the blood sugar are made. If symptoms develop during this period, they can be promptly reversed by intravenous glucose. The islet-cell tumours responsible for this picture of spontaneous hypoglycaemia are as a rule adenomas, but some are carcinomas. The adenomas are usually small, often multiple, and most commonly located in the body and tail of the pancreas.[1]

Other syndromes associated with tumours that do not secrete insulin have recently become recognized. In 1955 R. M. Zollinger and E. H. Ellison[2] described the occurrence of severe peptic ulceration of the jejunum in association with such tumours, the ulceration apparently being related to a profound hypersecretion of gastric juice. So striking was the gastric hypersecretion that they referred to the "almost unbelievable levels of 12-hour nocturnal gastric secretion despite complete vagus section and radical gastric resection." In the following year Ellison[3] reviewed the clinical and pathological features of 24 cases collected from the literature. Fourteen of these "ulcerogenic tumours" were single and ten were multiple. The majority of them were malignant but with a slow rate of growth, and peptic ulceration remained the predominant manifestation. "This new clinical entity consisting of a fulminating and frequently fatal peptic ulceration is characterized by excessive gastric secretions . . . and rapidly

[1] Whipple, A. O., *Surgery*, 1944, **16**, 289.
[2] Zollinger, R. M., and Ellison, E. H., *Ann. Surg.*, 1955, **142**, 709.
[3] Ellison, E. H., *Surgery*, 1956, **40**, 147.
[4] Dragstedt, L. R., *Arch. Surg. (Chicago)*, 1942, **44**, 438.
[5] Poth, E. J., and Fromm, S. M., *Gastroenterology*, 1950, **16**, 490.
[6] Verner, J. V., and Morrison, A. B., *Amer. J. Med.*, 1958, **25**, 374.
[7] Maynard, E. P., and Point, W. W., ibid., 1958, **25**, 456.

progressive, atypically located ulcers recurring despite adequate medical or surgical therapy." After resection of the pancreatic growth the gastric secretion falls to normal levels. This finding caused Ellison to suggest that a hormonal factor arising in the islet cells is capable of provoking gastric secretion. Since that time a considerable number of reports of the Zollinger–Ellison syndrome have appeared. Study of it seems likely to throw light on the aetiology of ordinary chronic duodenal ulcer, in which there have been some suggestions than pancreatic factors may play a part.[4,5]

Reports have now appeared on gastro-intestinal disturbances other than peptic ulceration which can occur with pancreatic tumours that do not secrete insulin. J. V. Verner and A. B. Morrison[6] describe two patients with refractory watery diarrhoea and resultant severe hypokalaemia, which was fatal, in whom such tumours were found on post-mortem examination. Hypokalaemia readily occurs with profuse diarrhoea, and in these patients it gave rise to renal failure, itself a well-known complication of potassium depletion. They also review seven cases of a similar nature collected from the literature, and they conclude: "Whatever relationship may exist between pancreatic islet cell adenomas and peptic ulceration, certainly diarrhoea is a prominent symptom in many patients with such tumours. Peptic ulceration, when present, appears considerably later than the diarrhoea which, if untreated, may itself bring about death from potassium deficiency and renal failure." E. P. Maynard and W. W. Point[7] describe a patient who presented with the "malabsorption syndrome," with steatorrhoea as a prominent feature, and who was treated for this for nearly five years before he was recognized as having an ulcerogenic pancreatic tumour. At operation a large tumour was found in the body of the pancreas and a metastasis was present in the liver. Examination of biopsy specimens showed it to be a well-differentiated tumour "consistent with carcinoma of the islets of Langerhans." The patient had excessive gastric secretion, with a basal secretion of 600 ml. an hour of juice containing 104 clinical units of free hydrochloric acid and with a *p*H of 1. The authors suggest that this large volume of gastric juice containing much hydrochloric acid might have produced a low *p*H in the small intestine, thereby inactivating the pancreatic enzymes (which become inoperative at *p*H 4.5 or lower) and producing in effect a pancreatic steatorrhoea.

It may be advisable to discard the term "ulcerogenic tumour of the pancreas" as a synonym for the Zollinger–Ellison syndrome, because peptic ulceration can no longer be regarded as an essential feature of the condition. It is plain that a non-insulin-secreting tumour of pancreas must enter into the differential diagnosis not only of severe peptic ulceration but also of chronic diarrhoea, including those examples in which there is evidence of the malabsorption syndrome. Once suspicion is aroused, the finding of considerable gastric hypersecretion would point to the need for exploratory laparotomy, because at present the only hope of complete recovery lies in surgical extirpation of that part of the pancreas bearing the tumour. Unfortunately the tumours are frequently small and not recognizable at laparotomy. In such circumstances a partial pancreatectomy with removal of the body and tail may be justifiable in so far as it may avert total gastrectomy. In other words, total gastrectomy becomes a second line of defence and one which is inferior to removal of the primary cause.

HAZARDS OF MASS RADIOGRAPHY

The Medical Research Council's report on the hazards of radiations[1] drew attention to the risks of diagnostic radiology. It concluded that the time had come "for a review of present practice." Thereupon a Government committee was set up for this purpose under the chairmanship of Lord Adrian, who has briefly described its aims.[2] Last week the Adrian Committee issued an interim report on mass miniature radiography of the chest,[3] and its main conclusion is expressed in these words: "The value of mass miniature radiography is so great that it must not be curtailed without good cause and we think it important therefore to state now that these examinations, properly conducted, make a negligible contribution to the total radiation to which the population is exposed."

Clearly much depends on what the committee means by the epithet "negligible," and it takes some care to explain it in the following sentence: "We do not, however, know enough about the effects of very small doses, and in stating that the danger of a particular form of examination is negligible we mean that the potential harm is negligible in comparison with the benefits." The benefits are mainly in the detection of previously unsuspected tuberculosis, though other diseases are also discovered. The report records that in 1957 about 4¾ million mass miniature radiography examinations were made in Great Britain, and these led to the discovery of 17,835 cases

[1] Medical Research Council, *The Hazards to Man of Nuclear and Allied Radiations*. 1956. H.M.S.O., London.
[2] Adrian, Lord, *Brit. med. J.*, 1957, **1**, 1180.
[3] *Radiological Hazards to Patients*. Interim Report of the Committee. 1959. H.M.S.O., London. 1s. 3d. net.
[4] *The Times*, April 29.

of pulmonary tuberculosis requiring supervision. Among 63,000 other abnormalities detected were 2,362 cases of lung cancer, 9,400 cases of pneumoconiosis, and nearly 12,000 cardiac abnormalities. Even so, there are conflicts of opinion on the best ways of using mass radiography nowadays to detect tuberculosis. Professor Gordon M. Fair, of Harvard University, expressed an interesting view last week at the Royal Society of Health's congress; as reported, he said,[4] "Routine mass *x*-ray surveys of the population may do more damage than good in communities in which tuberculosis is comparatively rare." The best way of using mass radiography machines to detect lung cancer is also being critically studied at present, and a paper by Dr. E. Posner and colleagues at page 1213 of the *Journal* this week is an interesting contribution to the problem. They are led to conclude that the chief emphasis must be on preventive measures such as reduction of tobacco smoking and not on the possibility of early diagnosis by mass radiography, though they recommend that more facilities for static mass radiography should be provided.

Against the useful results of mass radiography the Adrian Committee had to weigh the risks of the procedure. These are of two kinds—to the race through harmful genetic mutation in the reproductive cells of ovaries and testes, and to the individual by inducing leukaemia. The first is related to the dose of *x* rays reaching the gonads and the second to the dose reaching the bone marrow. The doses given in mass radiography are small even in comparison with those emitted by natural rocks such as granite. Data collected by the committee on the dose to the gonads show it to be smaller than had previously been estimated, and the committee considers mass radiography to be "a relatively unimportant source of gonadal radiation exposure." On the question of leukaemia the committee finds that indefinite continuation of mass radiography at the present rate could produce annually at the most 20 cases of leukaemia in addition to the present total of about 2,500, but might produce none. Put in another way, "An individual who has ten mass miniature radiography examinations over a series of years would have his chance of developing leukaemia in any year increased—if at all—from 50 in a million to at most 51."

While concluding that the benefits far outweigh the risks, the committee makes suggestions for reducing the risks still further. It recommends, for instance, that children and pregnant women should not be subjected to mass miniature radiography, but, when necessary, examined by means of full-size films with strict limitation of field size. It adds that similar considerations apply to small adults unless the field size can be limited to the chest. Further, some technical measures are recommended to reduce the *x*-ray dose to the patient from mass radiography machines.

The report concludes by emphasizing, what every radiologist will endorse, that diagnostic radiology of any kind must be kept to the minimum. It goes on to suggest that "the level may be reduced appreciably without prejudice to the interest of the patient." Moreover a higher dose is needed for fluoroscopy on the screen than for radiography on the photographic film, which, says the report, "is not generally realized even among the medical profession."

CANCER RISKS OF COSMETICS

The question of the cumulative toxicity of azo and other synthetic dyes used in the manufacture of lipstick was recently raised in the House of Lords.[1] Though some of the dyes in lipsticks must be absorbed by ingestion and by penetration through the skin,[2] they are not yet controlled as are colouring materials in food. The use of synthetic dyes in food is now controlled by a Statutory Instrument[3] based on recommendations of the Food Standards Committee of the Ministry of Agriculture, Fisheries, and Food.[4] Thirty synthetic colours are allowed as food additives, of which none are known or suspected carcinogens.

Cosmetic dyes and pigments are numerous. A German list[5] includes 184 colours; there are probably more in other countries, and the list does not include hair dyes. To test all these substances for toxic effects would be an expensive and difficult undertaking. However, the principle of having lists of permitted substances as opposed to lists of prohibited substances has been generally accepted for colours and other additives used in food. It might well be applied to cosmetics in order to reduce the carcinogenic hazard from them.

Apart from the dyes there are other constituents of cosmetics which may be considered as carcinogenic or toxic in other ways. Among these are the oestrogens, which cause cancer in animals and probably in man. The possible danger from either natural or synthetic oestrogens needs to be seriously considered. If oestrogens are administered under medical supervision, then the doctor has to decide whether the advantages of treatment with them are worth the risk which it entails. But the consumer of a food or the user of a cosmetic preparation cannot be expected to evaluate the advantages and risks of carcinogenic ingredients.

The carcinogenic hazard differs from other dangers in being insidious and delayed, because the latent period for inducing cancer in man is probably more than twenty years, whereas other toxic reactions such as dermatitis occur within a short time and often in such

[1] *Brit. med. J.*, 1959, **1**, 1192.
[2] Ibid., 1958, **2**, 38.
[3] S.I. No. 1066, 1957.
[4] See *Brit. med. J.*, 1955, **1**, 158.
[5] *Mitteilung Kommission zu Bearbeitung des Lebensmittelfarbstoffproblems*, Vol. 3, 1952.

a way that the cause can be recognized and removed. The carcinogenic stimulus, which is irreversible, is unlikely to be observed at the time, so that identification of a specific cause is peculiarly difficult. The difficulty of identification is increased because many of the carcinogens have remote actions on many different organs instead of a direct action on the skin or lips. That there is no safe dose of a carcinogen is a prudent assumption for several reasons, including the difficulty of determining the threshold dose, if indeed a threshold dose exists. Obviously no food or cosmetic should be allowed to carry the slightest risk of causing cancer. There is much to be said for controlling carcinogenic substances either by the legislation relating to poisons or by other means.

STRONTIUM-90 IN FOOD AND BONE

The Prime Minister was asked last week in Parliament whether the figures for any particular type of radiation to which human beings are now exposed were approaching the danger level. To amplify his brief reply Mr. Macmillan circulated a statement, which is reproduced in our Parliamentary report at page 1248. The statement is concerned with the fall-out of radioactive materials resulting from test explosions of nuclear weapons. Of these materials "strontium-90 merits the most immediate attention."

The rate of deposition of strontium-90 in rainfall in the United Kingdom has approximately doubled since May, 1958. By how much is the rate likely to increase in the future? The Parliamentary statement explains how difficult it is to give an adequate answer to this question. For one thing, methods of estimating the amount of radioactivity in the "stratospheric reservoir" are unreliable, and, for another, knowledge is lacking about the mechanism by which the stratospheric reservoir is depleted. The United States Department of Defence has recently suggested that the length of time radioactive materials remain in the stratosphere is shorter than was at first calculated. If this were true, it would mean that amounts of radioactive material present in the stratosphere have been overestimated, since there will be less to come down. It would also mean that radioactivity would have less time to decay before the material was deposited. But, as the statement points out, strontium-90 decays so slowly (its radioactive half-life is about 30 years) that the difference would be very small.

The fact that 1958 was a "bad" year for fall-out in Great Britain may have been due in part to the heavy rainfall throughout the year and in part to the "injection" of fission products into the stratosphere in high latitudes by the U.S.S.R. rather than into equatorial regions, where the U.S.A. and Britain operate.

According to the Prime Minister's statement, the quantity of strontium-90 in human diet in the United Kingdom rose much less in 1958 than did the rate of deposition. Dairy produce, particularly milk, is the source of most of the strontium-90 consumed in food. The accumulation of the isotope in milk is related mainly to the rate of deposition in the immediate past and not to the total deposition since fall-out began. If the increased rate of fall-out which began in the middle of 1958 continues, then, as the statement notes, an increase of the strontium-90 content of the diet is to be expected.

Strontium-90 is deposited and retained in bone. Measurements made several years ago by a committee of the Medical Research Council[1] showed that the amount found in human bone was about a thousandth of the maximum permissible level laid down by the International Commission on Radiological Protection for those who are occupationally exposed. The committee recommended that immediate consideration would be required if the concentration in human bones should show signs of rising beyond one-hundredth of the maximum permissible occupational level. According to the Prime Minister's statement, "the concentration in human bone of strontium-90 attributable to what has already been injected into the stratosphere is likely to remain below that at which immediate consideration would be necessary." This forecast would be more reassuring if we knew that international agreement was going to be reached on stopping the weapon tests.

[1] *The Hazards to Man of Nuclear and Allied Radiations*, 1956. H.M.S.O., London.

SAFE INDUSTRIAL ENVIRONMENT

One step in ensuring the safety of men working with dangerous chemicals is to restrict the concentration of the substance in the working atmosphere to a level below that considered likely to cause any toxic effects even after long exposure. The problem of deciding what is the "maximum allowable concentration" (M.A.C.) of a potentially harmful vapour or dust is not simple. For several years American experts in industrial hygiene have published lists of such M.A.C.s. They are modified as experience is gained, and this may come from improvements in analytical techniques, studies in experimental animals, or observations on men exposed to different working conditions.

In recent years it has become known that the M.A.C.s recommended by Russian industrial hygiene experts have for some substances been very much lower than those either proposed by the U.S. experts or accepted in other Western countries. As a first step towards understanding the reason for these differences and perhaps reconciling them, a symposium was recently held in Prague.[2] Representatives from 21 countries were present and papers on a wide range of problems in industrial hygiene were presented. It was clear that the differences in the M.A.C.s proposed could largely be explained by differences in the techniques employed to determine the toxicity of the materials towards experimental animals. The Russians and workers in some other East European countries study "higher nervous activity" by means of conditioned and other reflexes, and find that in some cases the concentration of a substance such as dichlorethane that will disturb these reflexes is much smaller than that needed to produce toxic effects such as narcosis or liver damage

[2] April 14-17. Chairman, Professor R. Truhaut (Paris). Organized by the Czechoslovak Association on Occupational Health.

or failure to grow. Even simple irritants such as sulphur dioxide have effects on behaviour at levels below those needed to produce pathological evidence of irritation of the respiratory tract. In some cases —beryllium is an example—there was no difference between the safe levels proposed in the U.S.A. and the U.S.S.R.

The interpretation of the findings in this new type of test on animals for toxicity is by no means clear. Not all the effects observed on "higher nervous activity" may indeed be harmful. Behaviour studies on animals are coming to the fore in other fields, such as pharmacology. Parallel studies on the behaviour of men exposed to toxic materials will probably be undertaken, and any effects observed may then be correlated with such objective signs as the excretion of the metabolites of the toxic material ingested. The prevention of poisoning in industry depends upon many things as well as opinions on the M.A.C., but the different views emphasized in this international symposium offer an interesting challenge and, it is to be hoped, an additional opportunity for collaborative study in a peaceful field.

GONORRHOEA INCREASING

A notice sent from the Ministry of Health to local health authorities last week draws attention to the increase in gonorrhoea in recent years.[1] The number of new cases seen at clinics has been rising steadily. The latest figures available show an increase between 1951 and 1957 of 31% for men and 53% for women, the total numbers of each in 1957 being 19,615 and 4,737 respectively.[2] This presumably reflects a real increase in the prevalence of the disease and not merely a higher proportion of patients coming for treatment, though, owing to successive infections in one individual, the numbers of new cases reported may be considerably lower than the numbers of new individuals affected. The increase in prevalence has been noted in many parts of the country, and particularly in London, but the trend has been downwards in a few urban areas—for instance, Tyneside—where immigrants and casual labourers are not very numerous. Though the number of women known to be infected is much less than the number of men, the proportion of infected women who go untreated is probably higher owing to the well-known fact that the infection is often less obvious in them. Even so, the Ministry expresses some anxiety about the apparent enlargement of a relatively small group of promiscuous infected women who constitute "a most important factor in spreading the disease."

No doubt several reasons account for the increase of infection. The idea that penicillin had made gonorrhoea a brief, trivial infection is still widespread, though entirely mistaken; strains of more or less resistant gonococci are being detected with increasing frequency. Again, various social factors must affect the epidemiology of any venereal disease, in particular the mobility of the population. There would still seem to be a need for educating the lay public in the nature of the disease and the necessity for obtaining thorough treatment of it. The medical and social aspects of gonorrhoea might be a less attractive subject to present to newspaper readers than the separation of Siamese twins, but the attempt would be likely to have a greater effect on health and happiness.

[1] Circular 6/59.
[2] *Report of the Ministry of Health for the Year 1957*, Part II, 1958. H.M.S.O., London.

WELLCOME RESEARCH LABORATORIES

On May 1 Sir Henry Dale, chairman of the Wellcome Trust, opened four new buildings at Beckenham to extend the resources of the biological division of the Wellcome Research Laboratories. The buildings represent the first two phases of the Wellcome Foundation's £2m. development scheme there; a third phase is to follow. All the new buildings are now in use, and a start has been made with the final phase. Indeed the first building, designed for the annual production of 4 million doses of poliomyelitis vaccine, a target now achieved, was completed over two years ago.[1] It is a handsome, three-story building equipped for the high standards of sterility needed in making this vaccine. The air intake is not only filtered, and heated or cooled, but is supplied at varying pressure gradients and from entirely separate systems to prevent the contamination of sterile suites or cross-infection between them. The polio building (phase 1 of the plan), which provides 25,000 sq. ft. of floor space, cost £250,000. The second phase comprises three roughly similar buildings, providing together 80,000 sq. ft. of floor space at a cost of £800,000. One building is for the production of virus vaccines such as those against yellow fever, influenza, and canine hepatitis; the second is for research and development work on viruses of medical or veterinary importance, while the last building is for the department of anaerobic bacteriology, which makes vaccines used in veterinary medicine. The final phase, begun last December, will provide buildings for the large-scale production of antitoxins and antisera and a new home for the pharmacology laboratory.

Sir Henry Dale said the opening was a great occasion for him. It must have been. For it was in the earlier Wellcome Physiological Research Laboratories some 50 years ago that Dale and Barger began their famous researches on ergot. It must have given Sir Henry special pleasure to open these fine new buildings for the Foundation's present research director, Dr. D. W. Adamson. To very few is it granted to see their first enterprises so augmented and developed. The benefits these great laboratories will bring to the science of immunology, and through that to the practice of human and veterinary medicine, cannot be counted: they will add their quota to the immeasurable sum of human health and happiness.

[1] *Brit. med. J.*, 1957, 2, 1188.

The next session of the General Medical Council will open on Tuesday, May 26, at 2.15 p.m., when the President, Sir David Campbell, will take the chair and deliver an address.

Drug Treatment of Disease

TONICS

BY

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Fashions change in drugs as in diseases, and it cannot be denied that tonics have acquired a distinctly old-fashioned flavour. People no longer seek toning-up because they feel slack; on the contrary, their friends compliment them on their good health when they look relaxed, and the general wish is for something which will promote this desirable state of hypotonia. However, the word tonic must not be taken too literally, since, with the possible exception of strychnine, none of the ingredients of the traditional tonic has the pharmacological effect of increasing tone. Perhaps a tonic is best defined as a preparation given to promote a feeling of well-being; under different circumstances, therefore, it may contain drugs which stimulate and drugs which soothe.

The layman regards a tonic as a medicine which speeds up the process of recovery from serious illness or operation or from the exhaustion of chronic anxiety and overwork, and he may also expect it to increase his resistance to disease. He may be right inasmuch as his health depends partly on the state of his mind, which in turn may be influenced by his faith, but there is no pharmacological basis for his beliefs. It is true that vitamins, hormones, and minerals such as iron do correct the metabolic fault of patients who lack them, but such powerful remedies should be used as specific therapy and not as part of a general tonic. To use them in blunderbuss fashion is always wasteful and occasionally harmful.

Glycerophosphates

These were originally prescribed in the early days of biochemistry when it was discovered that the lecithin in the central nervous system contains its phosphorus in this form. There is, however, no evidence that glycerophosphates taken by mouth exert any pharmacological or metabolic effect whatever, and probably their only virtue is that they are non-toxic and do no actual harm. They form the basis of some of the expensive proprietary tonics still widely taken.

Strychnine

This was the most popular of the older tonic drugs, and indeed Hutchison (1926) stated that nux vomica was at that time "perhaps the most widely prescribed drug in the pharmacopoeia." One may well wonder whether in another thirty years it will still be prescribed at all, since proof is lacking that in therapeutic doses it has any pharmacological effect except perhaps as an aperitive "bitter." However, of the traditional tonics a mixture containing nux vomica and perhaps another of the bitters such as gentian is probably as good as any and has the merit of being cheap and harmless. A suitable prescription is:

Sodium bicarbonate	10 gr. (0.6 g.)
Tincture of nux vomica	5 minims (0.3 ml.)
Infusion of gentian to	½ oz. (14 ml.)

Taken in water three times daily before meals.

Iron

This was included in many of the older tonics such as Easton's syrup (syrup of ferrous phosphate with quinine and strychnine) and was no doubt responsible for any lasting benefit resulting from them. It is probably wiser, however, not to prescribe such iron-containing mixtures as general-purpose tonics. Iron is of benefit only to those who need it and should be administered to them in the preparation most likely to be quickly efficacious when the cause of the deficiency has been established or is at least under investigation. If taken indiscriminately by patients vaguely off colour it may delay the diagnosis of a bleeding ulcer or cancer of the alimentary tract by temporarily correcting the anaemia; if the patient is not short of iron, its only possible effect is a needless digestive upset.

Vitamins

The administration to undiagnosed pale people of vitamin B_{12} or liver extract injections, or oral preparations containing liver, folic acid, or hog's stomach extract, either alone or, even worse, combined with other haematinics, must be roundly condemned, since this hinders the diagnosis of pernicious anaemia, prevents its efficient, supervised, and lifelong therapy, and so encourages the development of the permanent changes of subacute combined degeneration of the spinal cord.

The claim that vitamin A, usually taken combined with vitamin D in halibut liver oil capsules or cod liver oil emulsions, will raise resistance to infections such as the common cold is not supported by the facts, and, though these vitamins are toxic only if very large doses are taken, much of their considerable cost might well be saved without endangering the public health.

There is no scientific warrant for giving any of the vitamins as a general tonic, but there are of course many indications for their administration to patients who are convalescent or suffering from chronic diseases. Thus, there may be inadequate intake of vitamins from restricted diet, poor absorption as a result of gastro-intestinal disease, impaired synthesis in the gut due to antibiotic therapy, or increased metabolic requirements resulting, for example, from barbiturate therapy.

The toxic effects of chronic barbiturate intoxication (depression, mental confusion, slurring of speech, nystagmus, and ataxia) may be related to the fact that barbiturates retard carbohydrate metabolism by inhibiting pyruvate oxidation, and during long-term barbiturate therapy it is probably wise to give vitamin B complex—for example, tab. aneurin. co. fort., *B.N.F.*, which contains aneurin (thiamine) hydrochloride 5 mg., riboflavin 2 mg., nicotinamide 20 mg., and pyridoxine 2 mg. Moreover, toxic confusional states, whether due to barbiturate poisoning or other causes, sometimes clear up rapidly after the intravenous administration of vitamins B and C in large doses—for example,

"parentrovite," two ampoules of each of the high-potency mixtures, which are mixed together before injecting, containing aneurin hydrochloride 500 mg., riboflavin 8 mg., pyridoxine 100 mg., nicotinamide 320 mg., and ascorbic acid 1 g. in 20 ml. But these are specific indications. Vitamins are not tonics.

Alcohol

The earliest drug used by man for inducing a sense of well-being was alcohol, and for general purposes it is probably still the best. There can be little doubt that it is the favourite tonic prescribed by doctors for themselves or their colleagues. There are of course important contraindications, notably liver disease and gastro-intestinal disorders, and it is unwise to recommend the use of alcohol to people of unstable or self-indulgent temperament or to those oppressed by feelings of inadequacy.

Amphetamine Sulphate

This is a powerful stimulant of the central nervous system, increasing mental activity and making the patient feel more energetic and cheerful. Optimum dosage must be found for each individual and it is wise to start with 2.5 mg. by mouth, if necessary increasing the dose to 10 mg. two or three times daily. Idiosyncrasy is occasionally seen, a state of acute excitement bordering on mania being induced by as little as 10 mg. Side-effects are common and include dryness of the mouth, headache, restlessness, insomnia, and loss of appetite, and the well-being induced by the drug is sometimes followed a few hours later by an increased feeling of fatigue. However, it is a useful drug for the treatment of depression during convalescence, and, though it may be habit-forming, withdrawal after prolonged administration does not induce severe physical symptoms such as occur with the true drugs of addiction. There would appear to be no significant difference in the clinical effects of amphetamine and dexamphetamine.

Methyl Phenidate Hydrochloride ("ritalin") is a central nervous stimulant like amphetamine, but does not have the sympathomimetic actions of the latter and so does not raise the blood pressure. It is also said to cause less restlessness and tension. On the other hand, it is usually not so effective in improving the patient's sense of well-being. The dose is 10 mg. twice daily, and, like amphetamine, it should not normally be given after 4 p.m. or insomnia may result.

Pipradrol Hydrochloride ("meratran") is very similar in its actions and clinical effect to methyl phenidate and is given in doses of 2 mg. two or three times daily. It is doubtful if these two drugs have any important advantages over the more familiar and very much cheaper amphetamines, but they may be given a trial when the latter cause troublesome side-effects.

Tranquillizers

These drugs have been discussed previously in this series (Sargant, 1958; Vogt, 1958), but brief reference may be made to the value of combining a sedative such as the short-acting barbiturate amylobarbitone with amphetamine. This combination suits patients who are tense, anxious, and low-spirited better than either drug alone. Average doses are amylobarbitone 32–64 mg. (½ to 1 gr.) and amphetamine 5 mg., but there is wide individual variation of response to both drugs, so that the dose of either or both should be changed until the best effect is achieved. Proprietary tablets containing the two drugs, though convenient, are expensive and do not permit this fine adjustment in dosage.

Conclusion

Tonics may be helpful in making a patient feel temporarily better, but they cannot restore vitality destroyed by chronic anxiety and overwork or take the place of adequate convalescence after serious illness. They should not be a vehicle for specific remedies used indiscriminately and are usually none the worse for being simple and inexpensive.

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ROYAL SOCIETY OF HEALTH

CONGRESS AT HARROGATE

The 66th Health Congress, convened by the Royal Society of Health, was held at Harrogate from April 27 to May 1 with Lord COHEN OF BIRKENHEAD as its president and an attendance of over 3,000. This year, after the inaugural sessions, the Congress broke up into eleven specialist sections to debate subjects ranging from radiation protection to the press and health education. There were also the customary meetings of the five conferences. The conference of medical officers of health discussed the notifiable infectious diseases.

Intangible Returns for Health Expenditure

In his inaugural address Lord Cohen said that, whilst it was known that this country spent over £600m. a year on its National Health Service, and that more millions were spent on private medical advice and purchase of drugs and other treatment, the income was in the intangible terms of health and happiness, which in turn determined productivity and our material prosperity as a nation.

Lord Cohen went on to review the great changes in demographic and disease patterns since the beginning of this century, and the triumphs of both curative and preventive medicine, whose results could be seen in the changed needs for hospital provision. These successes in the control of disease rested on a tripod of endeavour—prevention, cure, and research; and these in turn depended on two relatively modern ideas, the first that the body was a mechanism which could be investigated by the methods and instruments of physics, chemistry, and biology, and the second the concept of the "cause of disease." Recently the emphasis in causation had been shifting to the concept of "the seed and the soil," and the realization that specific factors were not in themselves sufficient causes but that ways of life also contributed to the genesis of many diseases. The triumphs of curative medicine stemmed largely from the recent additions to the therapeutic armamentarium, but, however effective the treatment of disease, the major contribution to the nation's health would rest essentially on preventive measures.

Irrationality of Public Response

The proviso was that those who would benefit should co-operate. However weighty the evidence might be, psychological factors must not be overlooked; public reaction was often irrational and bound up with emotion when the principle of freedom of choice for the individual seemed to be involved, as had been shown in the resistance

to fluoridation projects. Recently we had had the extraordinary effect of the death of a young footballer in gaining acceptance of poliomyelitis vaccination by young adults. There was clearly need for study of the method for obtaining public appreciation of the need for preventive measures.

This applied to the individual as well as the community. Cancer of the lung was increasing rapidly. It was now the commonest form of fatal cancer, being responsible in Great Britain for about 20,000 deaths a year. Each year the incidence increased by a thousand, and there was the strongest statistical evidence to show that the more cigarettes a man smoked the more liable he was to develop lung cancer: should not the prudent man accept this and act upon it?

Too Little Spent in Research

Turning to the third leg of his tripod—research—Lord Cohen said it was disconcerting to reflect that half the total hospital beds in this country were for the mentally afflicted, that 1 in 250 of the population now occupied a bed in a mental hospital, that 1 in 20 at some period needed psychological hospital care, and that 1 in 100 children was mentally defective. In this field there was great need for intensive research in the genetic and metabolic aspects. But research needed not only bright ideas but also money; the amount at present available to the universities, the Medical Research Council, and other official bodies was too little, and the deficiency was not met by the voluntary institutions which so generously supported research.

Sectional and Conference Meetings

Among the more topical subjects discussed in the Sections were hospital planning in relation to present trends in medicine (Dr. J. O. F. DAVIES), and the "hospital centre" (Professor T. MCKEOWN); the changing pattern of the mental health services (Dr. T. P. REES), the next steps in mental health (Dr. G. R. HARGREAVES), and the epidemiology of mental illness (Dr. E. H. HARE); radiation levels (Professor W. V. MAYNEORD), and nuclear protection in the design and operation of nuclear power stations (Mr. J. C. DUCKWORTH); industrial hygiene and air pollution (Dr. PHILIP DRINKER, of Harvard University); and vaccination against poliomyelitis (Dr. JONAS SALK, of Pittsburgh University). The Sections also held several symposia. These were on the press and health education, rehabilitation and resettlement of disabled people, consumer protection in foodstuffs, and the strengthening of family life.

The domiciliary nurses and midwives discussed the changing pattern of domiciliary care, while the health visitors debated the preparation and aftercare of children who go to hospital. The medical officers of health, as mentioned earlier, considered the notifiable infectious diseases, and the public health inspectors discussed some problems of insecticides.

Dr. Jonas Salk Honoured

During the Congress Lord COHEN presented Dr. JONAS SALK with a scroll of honorary fellowship of the Royal Society of Health. The proceedings ended with the congress dinner on the last evening.

Dr. J. F. Warin, principal school medical officer for Oxford, is alarmed about the effects of modern fashions in footwear on the feet of schoolgirls. In his report for the year 1958 he writes as follows: "The prevailing fashion in feminine footwear is dreadful from the health point of view. The absurd height of some heels and the, even worse, narrow pointing of toes must be detrimental to foot health and, in fact, even ordinary walking appears to be difficult in some of the worst specimens. The school medical officers have found many examples of teenage schoolgirls wearing these absurd and harmful shoes and, already, some have developed painful corns. These girls are ruining their feet; they are bound to suffer much pain in later life and will keep the chiropodists busy for many years to come."

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Esidrex (Ciba Laboratories).
Hydrosaluric (Merck Sharp and Dohme).

These are both preparations of hydrochlorothiazide, which differs chemically from chlorothiazide in that the double bond in the heterocyclic ring is saturated by two hydrogen atoms, and are supplied in tablets of 25 and 50 mg.

The actions of hydrochlorothiazide are qualitatively similar to chlorothiazide, and there is as yet no convincing evidence that these two compounds differ significantly in their diuretic or antihypertensive effect. But, weight for weight, hydrochlorothiazide is more potent than chlorothiazide. It is impossible to say exactly how much more potent it is, because the dosage required to produce a given effect varies from patient to patient, and in the same patient from time to time. In normal subjects hydrochlorothiazide is usually 10–12 times more potent than chlorothiazide, but in patients with congestive cardiac failure it may be less than 10 times or more than 20 times more potent. Like the parent compound, hydrochlorothiazide promotes an approximately equimolar loss of sodium and chloride, and it also increases excretion of bicarbonate and potassium.

It is indicated for the relief of oedema, in a dosage related to the severity of fluid retention. In congestive failure, for example, 50–150 mg. daily is appropriate, given as a single dose in the morning or in two divided doses at 8 a.m. and 2 p.m. Because of the possibility of potassium depletion, hydrochlorothiazide should preferably be given on alternate days or on 3–4 days each week together with a supplement of potassium chloride.

Hydrochlorothiazide also has a mild hypotensive action. This may prove of value when the compound is given alone, but is of more importance in potentiating the action of other hypotensive drugs, such as rauwolfia and ganglion-blocking agents.

From the available data at present it appears that hydrochlorothiazide has the same therapeutic action, the same relative freedom from toxicity, and the same liability to cause potassium depletion, with consequent increased sensitivity to digitalis, as chlorothiazide. The only striking difference is in the dosage of the two compounds.

N.H.S. basic price: esidrex, 100 tabs. 25 mg., 40s. 10d.; hydrosaluric, 100 tabs. 25 mg., 40s. 10d.; 100 tabs. 50 mg., 75s.

Medapsol (Imperial Chemical Industries).—This is diaminodiphenyl sulphoxide (D.D.S.O.), available for clinical trial in 0.1-g. tablets.

The sulphones, notably the parent diaminodiphenyl sulphone, for some years have been the standard for the treatment of leprosy. Alternatives to these are obviously desirable, and the related sulphoxides offer possible substitutes. Diaminodiphenyl sulphoxide, which approximates very closely to diaminodiphenyl sulphone in chemical structure and molecular weight, has in fact been shown to cause clinical and bacteriological responses in leprosy patients comparable to those caused by the sulphone. The tolerated dosages of the two compounds are closely similar, and the methods of treatment used have been the same.

During the first few months of treatment with the sulphoxide, anaemia and leucopenia may develop. The neuritis so often later evident under sulphone treatment does not occur. Drug fever, damage to kidneys and liver, and lepra reaction also have not been found to follow the use of the sulphoxide in leprosy. So far no contraindications to its employment have been suggested. Obviously in so chronic a condition long study over many years is necessary adequately to assess the value of any drug in the treatment of leprosy; the initial trials of D.D.S.O. at least are encouraging.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Muscle Pain after Short-acting Relaxants

SIR,—Muscle pains following short-acting relaxants, described in the article by Dr. R. A. L. Leatherdale and his colleagues (*Journal*, April 4, p. 904), are almost unknown following suxamethonium-modified electro-convulsive therapy. The large majority of psychiatric patients are ambulant, and a high incidence of muscle pains would therefore have been anticipated.

The dosage used to modify E.C.T. is similar to that which is mentioned for patients undergoing oral surgery —there must be some major factor which protects the psychiatric patient. The cold comfort of the conventional operating table may well be responsible. The degree of muscular relaxation produced by the short-acting drugs must eliminate all postural tone ; to place a patient in this condition on a metal table, separated by only 1 in. (2.5 cm.) of sponge-rubber, is surely unnecessary. The hospital bed used by psychiatrists for their treatments may well be the factor which prevents these muscle pains.

The higher incidence of pain in female patients could be explained by the suggestion that their more generous body curves are more distorted when relaxed against a rigid surface.—I am, etc.,

Bexley, Kent. G. I. TEWFIK.

Intermittent Suxamethonium Injections

SIR,—We were interested to read Dr. J. Bullough's letter (*Journal*, March 21, p. 786) drawing attention to the prolonged bradycardia which may follow the administration of suxamethonium (succinylcholine). Our attention had been drawn to this potentially dangerous phenomenon by a recent case, in which the patient had been twice anaesthetized with this technique.

A female aged 51 was to undergo the implantation of yttrium seeds into the pituitary fossa. She had advanced carcinomatosis, and was markedly hypercalcaemic (serum calcium 9.7 mEq./l.), B.P. 145/75 mm. Hg. Premedication was with pethidine 50 mg. and atropine 0.6 mg., given one hour previous to induction. Anaesthesia was induced with thiopentone 250 mg. and suxamethonium 50 mg. followed by oral intubation. Anaesthesia was maintained with nitrous oxide and oxygen, 5/2 litres. During this time a continuous E.C.G. recording was taken, which showed no alteration in cardiac rate or rhythm, and there was no alteration in the B.P. level. A second dose of 50 mg. suxamethonium followed by 2.5 mg. of decamethonium again produced no demonstrable cardiac effect. The patient's blood pressure fell steadily, reaching a stable level of 100/60 three-quarters of an hour after the commencement of the operation. One hour after the induction a third injection of suxamethonium was given, which produced a severe bradycardia. Before this injection her pulse rate was 86 beats per minute, which fell to 22 beats per minute 20 seconds after the administration of the suxamethonium. The rate returned to the pre-injection figure after 88 seconds. The E.C.G. complexes were unchanged. Five minutes later a further 50 mg. of suxamethonium was administered, a pulse rate of 88 per minute falling to 35 per minute 8 seconds after the injection was completed. A polythene cannula was then inserted into the right basilic vein with a Seldinger needle, and the tip of the cannula advanced to the region of the superior vena cava. A mixed venous blood sample was taken, and a further injection of 50 mg. of suxamethonium was given. The pulse rate of 75 per minute fell 26 seconds later to a rate of 45 per minute. At this time a second sample of blood was quickly taken. The pulse rate returned to 75 beats per minute in 58 seconds. Subsequent analysis of the blood samples showed no alteration in the serum electrolytes between the two samples.

The same patient required a further implantation of yttrium five weeks later. Her blood pressure was 140/90, and she was again hypercalcaemic. Her general condition had deteriorated, and her premedication consisted of pethidine 25 mg. and atropine 0.6 mg. Under E.C.G. control induction and intubation were effected with thiopentone 100 mg. and suxamethonium 50 mg. This produced no changes in cardiac rate and rhythm, nor did the blood pressure change. Maintenance was continued with nitrous oxide and oxygen, 5/2 litres. Subsequently only standard 50-mg. doses of suxamethonium were given throughout the period of operation. The second dose of suxamethonium produced no cardiac effect, but the third and fourth doses showed a bradycardia. Prior to the third dose of suxamethonium her pulse rate was 125 beats per minute, which fell 24 seconds after the suxamethonium injection to 57 per minute. A rate of 115 per minute was regained after 54 seconds. During this episode the blood pressure fell from 140/90 to 120/80. Prior to the fourth injection the pulse rate was again 125 beats per minute, which fell to 55 per minute 19 seconds after the suxamethonium injection. Forty seconds later the original rate of 125 beats per minute was regained. The blood pressure remained steady at 140/85 during this period. It was observed that there was nodal rhythm during the two episodes of bradycardia.

Following the fourth injection of suxamethonium, atropine 0.15 mg. was given intravenously, the pulse rate at the time of injection being 110 beats per minute. Five minutes later the rate had risen to 120 per minute, and a fifth dose of suxamethonium was administered. 22 seconds later a bradycardia of 93 beats was apparent but no nodal rhythm, the pulse rate returning to 120 beats per minute after 40 seconds. There was no change in the blood pressure. Atropine 0.6 mg. was then given intravenously, and the pulse rose from 115 per minute to 125 per minute over five minutes. The blood pressure was 150/90. A sixth dose of suxamethonium was given intravenously, and after 12 seconds the rate of the pulse fell to 100 beats per minute, and remained at this level until the operation was completed some 15 minutes later. There was no change in the blood pressure. It was of interest to note that, during the first operation, there was no prolongation of the normal duration of apnoea associated with the doses of the relaxant drugs that were given. During the second operation, however, where the bradycardia was not so marked, there was a progressive lengthening of the duration of apnoea resulting from the successive administration of standard doses of suxamethonium.

Though the paper by H. V. Martin (Symposium on Curare and Curare-like Drugs, Venice, 1958) is as yet unobtainable, we would agree with many of the points brought out by Dr. Bullough. However, we would like to point out that the bradycardia following upon the administration of successive doses of suxamethonium in our case could still be observed after the fifth and sixth doses of this drug. The administration of atropine in the premedication, even though it was given at an accepted time prior to the induction, did little, if anything, to abolish or modify the bradycardia, and the small intravenous dose of atropine appeared to have little effect. Even after 0.6 mg. atropine was given intravenously, a sixth dose of suxamethonium still produced a slowing of the heart rate. It would seem that sufficient protection in this technique may be obtained through the intravenous injection of at least 0.6 mg. of atropine before the second dose of suxamethonium though the

underlying processes are still active. The mechanism of this effect of suxamethonium, and the time relationship of its appearance, are somewhat obscure, and we hope to make them the subject of further animal and human investigation.—We are, etc.,

IAN VERNER.
CHRISTINA COMTY.

Postgraduate Medical School, London, W.12.

Cardiac Pain

SIR,—The article by Dr. William Evans entitled "Faults in the Diagnosis and Management of Cardiac Pain" (*Journal*, January 31, p. 249) has given needed emphasis to pitfalls in the detection and care of patients with clinical coronary artery disease. Dr. Evans's plea to understand the patient as well as his disease reveals a unique blend of the knowledge and experience of the specialist with the practical perspective and wisdom of the personal family physician.

I am impelled, however, to take issue with the statement (p. 253) that "a nitrite, like 'peritrate' . . . taken into the stomach was shown a quarter of a century ago to be no more effective than a placebo in the prevention of cardiac pain." On the contrary, our studies have shown that peritrate in proper dosage (20 mg. or more) taken *before* meals is capable of influencing favourably the electrocardiographic response to the Master two-step test in a majority of patients. Moreover, recent studies in our laboratory carried out by a double-blind technique have clearly indicated that patients with angina pectoris, performing standard exercise, can distinguish peritrate from placebo in more than 90% of the tests. Our observations have shown that some of the reputed clinical failures with this drug have resulted from inadequate dosage and neglect to instruct the patient to take the medication on an empty stomach—i.e., before meals.—I am, etc.,

U.S. Public Health Service Hospital, Staten Island, New York. HENRY RUSSEK.

Steroid Therapy in Heart Failure

SIR,—Drs. J. N. Mickerson and J. Swale (*Journal*, April 4, p. 876) ascribe their success in treating patients with chronic congestive cardiac failure with prednisolone to anterior pituitary failure. These authors suggest that cardiac failure leads to anterior pituitary-adrenal stimulation, which later leads to "adrenal-pituitary exhaustion."

The syndrome they describe is well known and occurs in many other disease states: pigmentation (including buccal pigmentation), hypotension, and hyponatraemia not infrequently accompanying cachexia whatever the cause. On the basis of this clinical picture, the low urinary output of total oxogenic corticosteroids (Norymberski), and the considerable increase in the output of these steroids after corticotrophin, a state of hypopituitarism was postulated by Shuster.[1] There was no histological abnormality of the pituitary glands and the term functional hypopituitarism was therefore applied to this syndrome. The increased pigmentation in contrast to the depigmentation of other hypopituitary syndromes was taken to indicate a partial hypopituitarism involving corticotrophin but not melanocyte-stimulating hormone. Increased pigmentation would then result from withdrawal of the inhibitory influence of cortisol on the melanocyte-stimulating hormone. The patients actually studied[1] had tuberculosis or bronchogenic carcinoma, but the view was expressed that this pattern of corticosteroid excretion was probably common to the terminal stages of many diseases, and possibly related to cachexia.

The observations of Drs. Mickerson and Swale appear to confirm this earlier work, although it is often difficult to be certain of basal urinary corticosteroid output in patients with congestive cardiac failure, since urine output as well as glomerular filtration influence this.[2] Evidence at present in preparation for publication indicates that hypopituitarism cannot account for the syndrome, since plasma cortisol concentrations in such patients (including several with cardiac cachexia) are normal or above normal at a time when urinary corticosteroid excretion is low. In the presence of cachexia (or renal disease) a low urinary corticosteroid output increasing after corticotrophin is not a reliable index of hypopituitarism.

In patients with oedema prednisolone and its analogues often produce a considerable diuresis, not infrequently immediately after the drug is stopped. As your annotation suggests (*Journal*, April 4, p. 910), the exact mechanisms responsible for this are still far from clear.—I am, etc.,

Medical Unit, The Royal Infirmary, Cardiff. S. SHUSTER.

REFERENCES
[1] Shuster, S., *Brit. J. Tuberc.*, 1957, **51**, 279.
[2] Hatfield, C. B., and Shuster, S., in press.

Pulled Elbow

SIR,—I was most interested in the article on "The Pulled Elbow," by Drs. B. W. Broadhurst and A. J. Buhr, in the *Journal* of April 18 (p. 1018). Ever since Green and Gay wrote their paper[1] I have been on the look-out for this condition, and on many occasions have been presented with a case. I have in fact had three in the last few weeks, one of them a doctor's son, and one in my own youngest child.

Under the heading "diagnosis," the authors state that reduction is associated with a palpable or audible click. This is undoubtedly true, and is characteristic of the condition, but they go on to state that they believe this click is a diagnostic sign of the condition and is as typical as that of McMurray's test on a patient with a torn meniscus. I would make two points—first, the click cannot be a true diagnostic sign: it is a confirmatory sign, as it occurs after the diagnosis has been made and during treatment, and it is the history and lack of supination which are the main basis for the diagnosis. Secondly, McMurray's sign is a relatively rare sign, and cartilage injuries are usually diagnosed in the quiescent stage, in my practice and that of my colleagues, by their history rather than by any particular physical sign.—I am, etc.,

Bristol, 8. M. P. MCCORMACK.

REFERENCE
[1] Green, J. T., and Gay, F. H., *J. Bone Jt Surg.*, 1954, **36A**, 655.

Pancreatitis

SIR,—Mr. M. A. Birnstingl in his admirable review of chronic pancreatitis (*Journal*, April 11, p. 938) succinctly describes the radiological changes demonstrable in the duodenal loop as a result of chronic pancreatitis. It is a pity, however, that he makes no mention of the changes on the lesser curvature of the stomach which may be seen in chronic, and during the subacute phases of relapsing, pancreatitis.

Infiltration and distortion of the mucosal pattern over the lesser curvature of the stomach associated with a greater or lesser degree of forward displacement have been noted in acute stages of relapsing pancreatitis.

The changes have been so marked that recently on two occasions in this hospital a tentative radiological diagnosis of an infiltrative carcinoma of the stomach has been suggested. In one case the inflammatory nature of the hard, fixed mass was mistaken at laparotomy for inoperable malignancy, and only the subsequent spontaneous remission indicated the true nature of the lesion.

It is perhaps unfortunate that over-emphasis in the literature on the radiological changes demonstrable in the duodenum has resulted in neglect of other signs which may be seen in the stomach. This perhaps arises from the lack of appreciation of the frequency with which chronic pancreatitis or relapsing pancreatitis occurs as a segmental disease, often involving a segment of the body or tail of the pancreas, leaving the pancreatic head and consequently the duodenal curve completely normal.—I am, etc.,

Department of Diagnostic Radiology, Royal Infirmary, Edinburgh. ERIC SAMUEL.

SIR,—Mr. M. A. Birnstingl (*Journal*, April 11, p. 938) has produced an admirable account of chronic pancreatitis. It is an interesting reflection on the rarity of chronic relapsing pancreatitis in this country that he was able to find only ten such patients in the files of 16 years at St. Bartholomew's Hospital. He says that "in view of the small number of cases and the variety of procedures adopted, it would not, generally speaking, be profitable to describe either the methods used [in treatment] or the effects achieved." He points out, however, that one patient was relieved for seven years and one for longer than seven years by cholecyst-jejunostomy. Lest by-pass operations on the gall-bladder be assumed to be more valuable than in fact they are, may I recall that two out of three patients in the recently reported Leeds series[1] treated by cholecyst-gastrostomy after an attack of acute pancreatitis suffered a relapse of pancreatitis within five years?—I am, etc.,

Scarborough. A. V. POLLOCK.

REFERENCE
1 Pollock, A. V., *Brit. med. J.*, 1959, **1**, 6.

Calamity Syndrome

SIR,—Diagnosis is the bugbear of psychiatrists, and any contribution in this field deserves our serious consideration. Professor Martin Roth's "phobic anxiety-depersonalization syndrome," introduced at the Royal Society of Medicine on February 10 (*Journal*, February 28, p. 579), adds yet another name to the list of traumatic neuroses, calamity syndromes, fright neuroses, and grief reactions which have been described in the past. To be acceptable it must be clearly distinguished by symptoms, aetiology, or pathology from these other states.

It is hard to see how the concatenation of three common symptoms, regardless of the presence of others, can be justifiably termed a "new clinical entity" (depressive, hypochondriacal, vasomotor, obsessional, and even hysterical and schizophrenic symptoms were found in Professor Roth's series). Anxiety is a necessary part of any phobia, and Ackner[1] has pointed out the variety of conditions in which depersonalization can play a part.

Regarding aetiology, Professor Roth finds that 83% of his cases followed one of a number of stresses—bereavement, sickness of friends or relatives, illness, or acute danger to the patient, severance of family ties, and domestic stress are listed, all common enough stresses in any group of psychiatric patients. But the question arises how frequently does the syndrome occur as a reaction to any one of these "calamities" and to what extent is it a specific reaction to the "calamity." In the course of investigating 65 patients who were admitted to the Bethlem Royal and Maudsley Hospitals with mental illnesses following the death of a relative, I have been able to find only six in whom depersonalization and phobias have concurred. Lindemann and Cobb,[2] in their study of grief reactions, noted feelings of "unreality" in a number of his patients, and the reluctance to maintain social relationships and activities described by them might be interpreted as "phobic" in origin. It seems likely that several of Professor Roth's cases are grief reactions of this type.

Finally, the validity of the syndrome should rest on the establishment of a clear pathological basis. Professor Roth may be unconvinced by Kardiner's views on the physiogenic and psychodynamic origin of the "traumatic neuroses," but the evidence which he presents to link his syndrome with the temporal lobes and the fashionable "reticular system" is equally unconvincing. Because depersonalization can be produced by stimulation of the temporal lobes there is no reason to believe that these are of paramount importance or even necessary to the production of the clinical state of depersonalization. Professor Roth himself admits that the electroencephalographic changes which he described were not significantly different from those of his controls, and the therapeutic response to thiopentone and superficial psychotherapy described by Dr. Arthur King can be as easily explained in terms of suggestion and other psychodynamic mechanisms as it can by recourse to "altered activity of the adrenergic arousal system."

The real value of this work derives, not from its demonstration of a new clinical entity, but from the light which it is likely to throw on the physiology, biochemistry, and psychology of the reaction to stress.—I am, etc.,

London, S.E.26. C. MURRAY PARKES.

REFERENCES
1 Ackner, B., *J. ment. Sci.*, 1954, **100**, 838.
2 Lindemann, E., and Cobb, S., *Ann. Surg.*, 1943, **117**, 814.

Protecting the Nipple

SIR,—I have recently seen two nursing mothers who had excoriation of the nipples and areolae exactly corresponding in size and shape to the gauze and mackintosh protective pad in their nursing brassieres. One patient was on the point of abandoning breast-feeding, owing to the discomfort and pain. Manufacturers should be able to produce, for mothers who need it, some protection which is impervious to liquid but not to air, on the lines of the latest nylon film baby pants. A small piece of gauze backed by such material should be quite sufficient. I am sure it would help more mothers to continue breast-feeding their babies, which some of us still consider the best form of infant feeding.—I am, etc.,

Tetchill, Near Ellesmere, Salop. E. JEAN HIGGIE.

Anaesthesia for Bronchoscopy

SIR,—Reactions to amethocaine and lignocaine can be severe, as illustrated in Dr. S. K. Gupta's article, when used in bronchography and bronchoscopy (*Journal*, March 14, p. 695). In all his five cases amethocaine was used, but in Cases 4 and 5 both amethocaine and lignocaine were used, Case 5 being almost certainly hypersensitive to lignocaine.

Since reactions to amethocaine are more frequent than with lignocaine, lignocaine lozenges, although equally unpalatable, followed by the application of lignocaine solution is preferable. However, one lignocaine lozenge (sucking half of which is sufficient) costs about 1s., as compared with approximately 1½d. for one amethocaine lozenge. Lignocaine lozenges can be prepared in hospital pharmacies for about 4½d. per lozenge, using 250 mg. of lignocaine hydrochloride and a *B.P.C.* base.
—I am, etc.,

Withington Hospital, Manchester, 20. I. A. KELLOCK.

Hypnosis for Patients with Burns

SIR,—We have read with interest the letter of Dr. O. H. E. Bayles (*Journal*, April 4, p. 923). In fact we have already done what he suggests, and we should like briefly to describe our experience.

The patient, a young man of 21, had 40% second- and third-degree burns of the arms, thorax, back, and left leg. He was anaesthetized and intubated in the usual way. He developed cardiac arrest shortly after, but was quickly resuscitated by cardiac massage, and recovered consciousness normally immediately after extubation. This case was similar to the one already reported by us (*Journal*, March 7, p. 624).

A week later the burnt hands required urgent grafting, and the use of hypnotic analgesia was considered for the forthcoming operation. The patient was approached, and, though terrified of both the operation and the hypnosis, he agreed to give the method a trial. He proved susceptible, was quickly hypnotized, and was trained to produce analgesia of arms and legs. Later the same day, split-skin grafts were taken from both lower legs and grafted to his hands. He lay quite still during the operation without pain or complaint. He was able to co-operate in keeping arms raised in the air for a while for the benefit of the surgeon. At no time did the heart give rise to anxiety, apart from a constant tachycardia, presumably due to the presence of residual fear and the burns injury.

Hypnosis, in fact, sufficed for premedication, operation, and post-operative analgesia.—We are, etc.,

B. L. FINER.
B. O. NYLEN.
University Hospital, Uppsala, Sweden.

Lipoma of the Broad Ligament

SIR,—The admitted rarity of lipomas of the broad ligament prompts me to publish the following case report.

On September 8, 1958, a woman aged 50 was admitted to the Civil Hospital, Port Louis, with a three-month history of persistent abdominal pain in the left iliac fossa accompanied by leucorrhoea. She had no other symptoms. Her past obstetric history revealed that she had had eight normal pregnancies and four miscarriages which had never been investigated but which she herself attributed to overwork during the early months of pregnancy. Her menopause had taken place without causing her any trouble three years previously. Her general condition was found to be good. Speculum and bimanual examination showed a healthy cervix and an anteverted, normal-sized uterus, but a tender, ill-defined mass was felt through the right vaginal fornix. At laparotomy, performed on September 16, a well-encapsulated lipoma of the right broad ligament measuring 6 × 5 in. (15.2 × 12.7 cm.) and weighing 12 oz. (340 g.) was found and enucleated. Recovery was uneventful.

Solid tumours in the broad ligament are generally uterine fibromyomata which have grown laterally between the peritoneal folds of the ligament, though occasionally such a tumour may be present without any obvious connexion with the uterus. On rare occasions tumours of this type have been found in the broad ligament, where they may attain a considerable size.[1] Visceral lipomas are stated to be rare, and the broad ligament an uncommon site.[2]

I wish to thank Dr. E. Losonczi, Director of Medical Services, and Dr. M. Shun Shin, under whose care the patient was admitted, for permission to publish this case.
—I am, etc.,

Mauritius. P. F. R. CANTIN.

REFERENCES
[1] Kerr, J. Munro, *Combined Textbook of Obstetrics and Gynaecology*, 1944, 4th ed., p. 1015. Edinburgh.
[2] Rogers, L. C., *Medical Annual*, 1954, p. 245.

Mummified Foetus

SIR,—The letter of Dr. Anne Hilliard in the *Journal* of February 14 (p. 437) in which she describes a mummified foetus in the uterus I found very interesting. Perhaps your readers may find the following case of interest.

In 1950 while medical officer in charge of the Victoria Hospital, Bathurst, Gambia, British West Africa, a Gambian woman about 35 years of age reported to my out-patient department because she had a tumour of the abdomen. She had not seen a period for 12 months, and was worried as she thought she was pregnant. She had not felt foetal movements for a long time (unable to say exactly). Her condition was good and she had no pains, only occasional discomfort in the lower abdomen.

I examined her and found a freely movable abdominal tumour about the size of a small football. A vaginal examination found the uterus to be very slightly enlarged. The tumour was free above it, and situated to the left. I performed a laparotomy, and found what appeared to be a cyst of the left ovary. This was removed. On opening this cyst a full-term mummified foetus was found in good condition. The mother made an uninterrupted recovery and returned to her village.

—I am, etc.,

Medical Department, British Transport Commission, Manchester. G. E. J. PORTER.

Children with Pneumonia

SIR,—May I have some more space to assure Professor Wilfrid Gaisford (*Journal*, March 7, p. 647) that if he visits my department he will not find acutely ill infants hanging over the sides of beds, as my letter (p. 647) may have suggested. We nurse infants with severe respiratory infections in incubators or cots, depending on their size, oxygen in the latter instance being given when needed by box or tent. When secretions are copious, postural drainage is given, first by alternating the infant's position from prone to supine and lateral, drainage of the lower lobes being achieved by head-down tilt of incubator tray or cot to 15 or 20°, for such time as the head nurse considers appropriate or is ordered by the medical staff; a head-up tilt is usually maintained for an hour or so after feeds to aid digestion and also drainage of the upper lobes. Older children are tipped in the usual manner by tilting the bed or tipping frame according to the predominantly affected area of lung. The less acutely ill young infants can so easily be tipped over the nurse's or mother's knee for short periods as indicated, particularly before feeds. The remarks on hanging over the side of the bed referred to the older child in the home, and I frequently advise practitioners or parents to encourage drainage of pulmonary secretions in this

way—for instance, in the child who will not cough effectively, or in the asthmatic who has difficulty in clearing his bronchi of viscid sputum. Ten minutes of postural drainage before retiring will in many cases enable a child (and his parents) to sleep undisturbed by irritating and ineffective cough.

In particular, in the very ill infant with copious secretions, where Professor Gaisford would seem afraid of postural drainage, judicious posturing and suction of the pharynx can be most efficacious, and it is not infrequent for my nurses to obtain 10 to 15 ml. of mucopurulent secretions within a few hours of admission, with marked relief of distress and cyanosis. In such cases, where partial blockage of the airways by secretion seriously impedes pulmonary ventilation, particularly in the constantly recumbent infant, I believe that postural drainage is the most effective method of freeing the airways and of preventing the segmental collapse which may follow unrelieved bronchial occlusion.

I feel sure that I am not alone in advocating the wider use of postural drainage, believing it to be just as rational in most cases of respiratory infection, where there are excess secretions, as in the more commonly accepted indications, such as in premature and newborn infants, patients with bronchiectasis, respiratory paralysis, or post-operative bronchial obstruction.—I am, etc.,

Galway. BRIAN MCNICHOLL.

Atony of the Female Bladder

SIR,—I was interested in Mr. H. S. Trafford's article (*Journal*, January 17, p. 149) on four cases of atony of the bladder. Like Mr. J. P. Mitchell (*Journal*, February 7, p. 365) I feel each case he describes seems to be a chronic urinary retention. I cannot agree with Mr. Trafford (*Journal*, March 7, p. 649) that chronic retention due to prostatic enlargement is invariably associated with some degree of upper renal tract dilatation, nor do I feel that the normal urea levels in his cases need necessarily be accounted for by atony of the bladder.

As a result of researches into chronic urinary retention in males,[1] I classify cases of chronic retention into three grades: (1) cases in which the upper urinary tract is normal or almost normal; (2) cases in which there is gross hydronephrosis; and (3) cases in which there is little or no demonstrable function. In all these groups, but especially in the middle group, the significance of the intravenous pyelogram findings may need to be "shaded," the blood urea being at variance with the *x*-ray findings. The blood urea level depends on several factors—the most significant one, as far as the present hypothesis is concerned, being the fluid intake. An adequate fluid intake can produce a normal blood urea in some of these cases.—I am, etc.,

Liverpool, 1. R. MARCUS.

REFERENCE

1 Marcus, R., *The Management of Chronic Retention*, 1949, M.D. thesis, Liverpool University.

SIR,—Dr. M. A. Dobbin Crawford's suggestion (*Journal*, March 21, p. 788) that atony of the female bladder can be due to a long-continued habit of voluntarily delayed micturition is an interesting one and may be near the truth. Certainly the signs of obstruction can usually be seen only by the eye of faith in these not uncommon cases.

A case that recently came under my care, however, suggests that the medical profession may not be altogether free from responsibility for this condition. A lady of 67 years of age, with complete retention of urine, and a bladder neck cystoscopically normal, gave the history that 20 years ago she had had an attack of "cystitis" and that her doctor had told her to drink at least four quarts (4.5 litres) a day. This advice she had obeyed religiously ever since.

It seems probable that the consequent flood of urine, dammed back on the innumerable occasions when it is socially inconvenient to empty the full bladder, may have gradually distended that viscus to the point where atrophy of the muscle fibres occurred.

It may be that the widespread policy of advising a forced fluid intake in all and sundry urinary conditions is not without its dangers.—I am, etc.,

Royal Victoria Hospital, Bournemouth. W. G. Q. MILLS.

Glycyrrhetinic Acid Ointment

SIR,—It looks as if glycyrrhetinic acid may become an important therapeutic agent in various fields. There is now a large literature in its favour in pharmacological, dental, and veterinary journals. Your annotation (*Journal*, April 4, p. 914) discusses its present position in dermatology, which is still unsettled. I should like to point out that a number of dermatologists in addition to those mentioned in the annotation have reported good results from the use of the ointment, and I append references to three such reports.[1–3]—I am, etc.,

London, W.1. E. LIPMAN COHEN.

REFERENCES

1 Cohen, E. L., *Practitioner*, 1958, **181**, 618.
2 Pozza, G., *G. ital. Derm. Sif.*, 1957, **98**, 191.
3 Zanchi, M., and Spagnoli, U., *Dermatologia (Napoli)*, 1957, **8**, 35.

Case Reports from the Bible

SIR,—From his authoritative letter (*Journal*, February 28, p. 585) Dr. T. Stephanides emerges as yet another victim of a frequent ailment in this analytic age—that of attempting to explain away the miracles related in the Bible on dubious scientific grounds.

His reasons for assuming that the snake which bit Saint Paul after his shipwreck on the Island of Melita (*Acts of the Apostles*, Chapter 28) was *Coluber viridiflavus* Lacepéde, as opposed to a truly venomous one, are very meagre, and are based on three misapprehensions. These are: (1) that if the snake had been a viper it would have fled; (2) that it hung on to Saint Paul; and (3) that the natives of the island mistook a harmless, though aggressive, snake for a poisonous one.

In answer to the first, it reads as no contradiction to me, a native of Australia, where snakes of many and varied species abound, to learn that a normally timid snake will attack the hand that is placing it in the fire. Indeed, one would expect it.

With regard to the hanging on, Mgr. Knox's translation of the passage runs: "... and the natives, when they saw the beast *coiled* round his hand, said to one another ..."

Finally, Dr. Stephanides suggests that the natives were wrong in thinking this was a venomous snake, which is surely an erroneous deduction. The local inhabitants of an area are usually those with the widest knowledge of local fauna, and can tell poisonous from harmless snakes with the ease of the experienced clinician making

a difficult diagnosis. That they expected Saint Paul to have "swollen and fallen down dead suddenly" clearly shows that they were familiar with the kind of snake concerned, and with the fatal consequences of being bitten by it.—I am, etc.,

Oxford. A. J. D. BRASS.

When to Tie the Cord

SIR,—I have read with interest the letter of Dr. W. N. Leak (*Journal*, February 28, p. 584). As an old student of Mr. Alan Brews I have recently re-read his eleventh edition of Eden and Holland and would like to draw attention to another reference to cord ligature in this manual.[1] In discussing the experiments of Barclay, Francklin, and Prichard on changes in the circulation after birth of the sheep foetus he states: "They estimated that in the interval between closure of the umbilical arteries and that of the ductus venosus about 100 ml. of blood was gained by the foetus from the placenta. (It should be noted in passing that these observations emphasize the importance of not clamping or tying the umbilical cord until several minutes after birth.)" I clearly remember being taught this as a student in the London Hospital.—I am, etc.,

Devonport. P. G. HARRIES.

REFERENCE

[1] Eden and Holland's *Manual of Obstetrics*, 1957, p. 64, 11th edition. London.

Kwashiorkor and Cirrhosis

SIR,—In reply to Drs. E. Kahn and H. Stein (*Journal*, August 16, 1958, p. 448), I would like to emphasize that prolonged fatty infiltration in kwashiorkor is the main fact which may lead to cirrhosis. It appears that there may be some other additional factor, as the severity of the clinical picture of the disease does not always bear a definite relation to hepatic damage.

P. M. Smythe,[1] in his article on changes in intestinal bacterial flora and role of infection in kwashiorkor, writes that an effect of inadequate protein diet is disturbance of intestinal flora and this plays a significant part in the clinical picture of kwashiorkor. He also writes that qualitative or quantitative alteration of bacteria that synthesize or metabolize vitamins and amino-acids may account for striking variation of severity and appearance of dermatoses, cheilosis, purpura, and megaloblastic anaemia in different cases in which patients are essentially on the same diet. Like Smythe, I think the fundamental aetiological factor in kwashiorkor is a protein-deficient diet. Kahn and Stein saw fewer cases of cirrhosis in kwashiorkor in African children. The same is the fact in Calcutta. We see fewer cases of cirrhosis in kwashiorkor than before, as we find skimmed milk very helpful in the treatment and has caused great diminution of mortality and morbidity.

Next, I have already written in my paper[2] that cirrhosis of liver in kwashiorkor rarely shows the clinical picture of fully developed cirrhosis, with hepato-cellular failure and portal hypertension, as seen in infantile cirrhosis in Indian children. The veno-occlusive disease is not the type of cirrhosis we find in Indian children as suggested by Kahn and Stein. The veno-occlusive disease differs not only clinically but histologically. Most of the cases of cirrhosis in Indian children are post-necrotic cirrhosis which M.V.R. Rao[3] described as subacute toxic cirrhosis.

My observation on infantile cirrhosis, which I have not yet published, shows most of them are the post-necrotic type, although true Laennec's cirrhosis, fatty portal cirrhosis, and primary biliary cirrhosis have been observed, and in none of them endophlebitis of central vein could be seen as stated above.—I am, etc.,

Calcutta. N. K. CHANDA.

REFERENCES

[1] Smythe, P. M., *Lancet*, 1958, **2**, 724.
[2] Chanda, N. K., *Brit. med. J.*, 1958, **1**, 1263.
[3] Rao, M. V. R., *Indian J. med. Res.*, 1935, **23**, 69.

Attempted Suicide

SIR,—A problem of increasing importance is presented by the rising incidence of attempted suicide, particularly due to barbiturate overdosage.

It is well known that certain districts in London, for example, have a high rate of attempted suicide, but it is very difficult to obtain any accurate figures. When I telephoned Somerset House for information, I was told, somewhat drily, that they only dealt with successful cases. Woodside[1] gives the figures for deaths by suicide in England and Wales in 1956 as 5,262, and the attempted suicides known to the police as 5,387 (the actual figure must be very much higher). She also states that during the year 1957 44 attempted suicides arrived at Guy's Hospital, 63% being due to barbiturate overdosage.

I have examined the admissions to New End Hospital, Hampstead, a district which has a notoriously high suicide rate, and find that from January 1 to December 31, 1958, there were 92 admissions for attempted suicide, a rate of two per week. Most of these attempts were due to barbiturate overdosage, and I feel that we should seek some means of prevention.

I have been told that there are now barbiturates on the market which contain a very small amount of bemegride, so that anyone taking an overdose will ingest a large quantity of bemegride to counteract the barbiturate, while there is not enough in the normal dose to interfere with the tablet's efficacy. Another suggestion is the inclusion of a small amount of emetic in each tablet so that an overdose produces emesis. The drawback is that we do not have any reliable statistics and so it is difficult to carry out a properly controlled trial of such drugs.

May I suggest that one way of overcoming this difficulty would be to make attempted suicide notifiable to the local medical officer of health? This would tell us where the cases are occurring and then we could take comparable districts and do a controlled series to see whether the reported rates decrease in the district under trial. It is also possible that these new preparations may be of use in controlling or preventing barbiturate addiction. We all prescribe these lethal weapons and to some extent share the responsibility for their consequences.

My thanks are due to Mr. J. Piery for permission to consult the records of New End Hospital.

—I am, etc.,

London, S.E.10. CYRIL FOX.

REFERENCE

[1] Woodside, M., *Brit. med. J.*, 1958, **2**, 411.

International Medical Qualifications

SIR,—Your leading articles on the G.M.C. and on the need for doctors overseas (*Journal*, November 22, 1958, pp. 1278 and 1279) brought to my mind the uneven distribution of doctors throughout the world.

There are many reasons for it, and the problem is obviously very complicated. However, very often there are difficulties in obtaining registration for a

practitioner from one country in another. An international medical degree acceptable all over the world would not only be of practical value to individual doctors seeking employment and to the countries which need them, but would also raise the standards of medical schools all over the world. A board of eminent doctors, acting under the auspices of the World Health Organization, would, in my opinion, be the best authority to grant these international degrees.—I am, etc.,

Medical Department, Tanganyika. I. LAUFER.

Molluscum Sebaceum

SIR,—May I make a comment on your interesting annotation on molluscum sebaceum (*Journal*, April 18, p. 1027)? Your annotator states "patients as young as 15 have been reported." In a short paper read at the annual meeting of the British Association of Dermatology in 1956 I described a case showing two lesions, one on each cheek. The lesions were excised and proved histologically. The case was that of a Pakistani baby girl aged 8 months. I believe this is the youngest case ever recorded.—I am, etc.,

Bradford. ALLAN BIGHAM.

Mysterious Dentine

SIR,—Your annotation entitled "Mysterious Dentine" (*Journal*, April 4, p. 913) recalls a further mysterious property peculiar to this tissue and which has been a source of puzzlement to me. The ability to translate "sweetness" as a stimulus of pain is a property of dentine shared by no other tissue, and the mechanism of this peculiarity has never been satisfactorily explained. Presumably, the high osmotic pressure of a sugar solution acting on exposed dentine is productive of a painful sensation, yet even a strong isothermic salt solution does not elicit a reaction from dentine.

That this is not only an academic problem is demonstrated by the fact that this source of pain is one frequently encountered, and is largely unresponsive to the palliative treatment which can be offered. Your plea for a combined team of research workers on this and related problems is indeed a pertinent one.—I am, etc.,

London, W.C.1. G. H. SPERBER.

Physiotherapy in Arthritis

SIR,—For years many dealing with the treatment of arthritis as a specialty have been aware that physiotherapy is of little use. There are cases of stiff knee-joints and certain other single joints where the application of diathermy (or rest and warmth) benefits; but this could be given more easily by other less expensive methods.

The skill of a good masseuse or masseur is very worth while in other medical fields, but it is wasted in arthritis, as mentioned by Dr. James Cyriax (*Journal*, March 28, p. 857). I am of the opinion that electrical stimulation of muscles is often actually harmful in arthritic cases. Passive movements can be organized and supervised by the physiotherapist; but active voluntary movements, with or without the pull of gravity, of the groups of muscles especially involved, often supplemented by augmented degrees of resistance, are the essential physical treatment of arthritis at certain stages of the condition.

It was heartening to read the excellent report by Miss D. E. Hamilton, Professor E. G. L. Bywaters, and Mr. N. W. Please in the *Journal* of February 28 (p. 542). I am often seeing, as are other rheumatologists, the excessive administration of dangerous drugs, hormonal and others, to arthritic cases, but unfortunately keen observation by clinicians in their specialty will give little good to the profession until some of the research teams can prove the observations statistically, often many years after the facts are known. Thus it was with gratification that I read the learned report of the research team headed by Professor Bywaters, and Dr. Cyriax's subsequent letter.—I am, etc.,

London, W.1. MARJORIE M. DOBSON.

Recurrent Phlyctenular Kerato-conjunctivitis

SIR,—May I comment on the article by Dr. Arnold Pines on "Recurrent Phlyctenular Kerato-conjunctivitis Treated by Desensitization to Tuberculin" (*Journal*, March 14, p. 689)? In 1907, when a third-year student, I suffered from this painful complaint for some six months, with no relief, having ulcer following upon ulcer, often four or five at a time on both eyes. After six months I did a Von Pirquet test, with one undiluted drop of old tuberculin (Lucius Meister-Bruning) scratch-hatched through the drop. It came up like a small tomato, and lo—my eyes ceased to pain. To demonstrate it to my consultant, who had scoffed at my query whether I was "strumous," I repeated the test about a week later, with similar result—and the ulcers and their tracks disappeared!

Since then, in general and surgical practice, I have always used this simple method, with invariable good results. Never have I bothered to inject with the unwieldy tuberculin syringes for injecting various "dilutions," nor ever done Mantoux tests, because the amount to be absorbed by the patient is much better measured by the length and amount of the scratching done through the solitary small drop. What I have found to matter is the quality of the old tuberculin used. When tested on known tubercular patients the old German stuff was always good, but during the two wars I had many disappointments. Nowadays I use fresh (clear water-white) mammalian P.P.D. from the Veterinary Laboratory, Ministry of Agriculture, Weybridge, and have to get it fresh every month.

Dr. Arnold Pines is to be congratulated, but his skill is possibly beyond the average, in dealing with the minute graduations of those pesky syringes. "Scratch, boy, scratch."—I am, etc.,

Bishop's Stortford, Herts. ROBERT A. R. WALLACE.

Food-poisoning and Food Hygiene

SIR,—Your leading article (*Journal*, April 18, p. 1023) makes very startling reading, and it is extraordinary that so many people avoid the hazards of food-poisoning. It is very disturbing to read that adequate sterilization of food and a "no-touch" technique are not used in every cooked-meat factory—surely the public are entitled to expect that the public health authorities will safeguard their interests in this matter.

Your reference to a "more liberal use of refrigeration" puzzles me—this will prevent, to use your own words, "unkilled germs from multiplying," or, put another way, the infected meats go bad in the customer's hands instead of the shopkeeper's. No, Sir, let the goods speak for themselves—if they are pure and clean, they will remain fresh without refrigeration.—I am, etc.,

London, N.7. CHARLES O. KENNEDY.

A Moral Obligation

SIR,—I am glad Dr. Frederick Dillon (*Journal*, April 18, p. 1041) has drawn attention to the case of Mr. A. H. Barber. This surgeon has suffered at the hands of a regional board, who were condemned by the decision of a High Court judge. Numerous protests have followed by eminent lay leaders and *The Times*. If the indifference of the profession at large has been staggering, the attitude of the British Medical Association has been disgraceful. We are in danger of repeating the same impolicy which worked such confusion at the time of the introduction of the National Health Act and again when resignation from the Health Services was first mooted. How long are we to tolerate the supreme control of a hospital by a regional board's oligarchy? We are entitled to know the reasons, if any, for the Association's silence and apparent indifference to a principle which is vital to our interests.—I am, etc.,

London, N.16. M. N. OSTER.

*** The B.M.A. has been neither indifferent nor silent about the case of Mr. A. H. Barber. In the early stages the B.M.A. was asked for help and was willing to give it, but on the facts then available it appeared that Mr. Barber had no right of appeal under clause 16 of the Terms and Conditions of Service. Only at the court hearing in 1957 did it become known to the B.M.A. that Mr. Barber's letter of appointment from the Manchester regional board differed from others, and in fact constituted a contract. Since the judgment, the B.M.A. has pressed repeatedly for Mr. Barber's reinstatement—by correspondence, interview with Ministry officials, and a deputation led by the Chairman of Council to the Minister himself. As a result of this, as we stated in our leader on March 14 (p. 703), both the Minister and the board have now accepted a "moral obligation" to assist Mr. Barber, though the Minister maintains he has no powers to by-pass the Appointment of Specialists Regulations and compel the board to reappoint Mr. Barber.—ED., *B.M.J.*

Student Suicides

SIR,—An aspect of the student mental health problem which is becoming increasingly important is that of "job security." Many students know from experience that universities fail as social institutions at this point. In social actuality, the student who fails in an examination, especially in a final examination, is in the same category as an unemployed worker. The unemployed worker is, of course, covered to a small extent, but the student may be weathering the economic storm unaided. The examiner and professor thus become not only an arbiter of a particular ability to probe a human spleen, and not only an assessor of a particular limited range of human knowledge, but also—and this is of fundamental importance—a sort of Ministry of Labour official handing out an employment certificate.

Unless universities show a greater social realism in this question of "job security," they are inviting replacement by a more psychologically wholesome type of technical education where every student has the emotional, intellectual, and economic security of a part-time job during his three or more years of training.

The assertion by Dr. N. B. Eastwood (*Journal*, April 11, p. 972) that students with intelligence quotients over 170 are not catered for at a university is alarming. Does it mean in effect that universities do not cater for universal minds? Why then do they call themselves universities?—I am, etc.,

Wolverhampton. GARETH R. DAVIES.

Musical Hazards

SIR,—Your anonymous 'cellist (*Journal*, April 11, p. 975) has my sympathy with his overbreathing troubles. I find that I am apt to overbreathe playing the 'cello either in public or privately, though I do not suffer from cramps, which I think, as your correspondent suggests, may be a direct result. I suggest he tries a few calcium tablets before a performance, but I feel sure this curious overbreathing when playing the 'cello is mainly a bad habit and should be tackled as such. Unfortunately any sedative whatever takes the edge off one's performance and even a little alcohol has a bad effect.

Personally I find the chief hazard in playing the 'cello is the development of what I strongly suspect is a traumatic arthritis of the terminal interphalangeal joints. To overcome the pain and disability when playing I have devised a little adhesive plaster strap which prevents hyperextension.—I am, etc.,

Eye, Suffolk. J. SHACKLETON BAILEY.

Telling the Cancer Patient

SIR,—There is one aspect of the question whether the patient should be told that he has cancer which I have not seen discussed (*Journal*, April 18, p. 1039). I refer to the economic aspect. If told in time the patient will be enabled to set his affairs in order, to make a new will, if necessary, to distribute assets to children, and otherwise conserve his estate. In fact one can envisage a state of affairs where not to tell the patient would involve the family in considerable loss. These considerations only further emphasize that each case must be considered on its merits and no hard and fast rule laid down.—I am, etc.,

London, E.C.1. A. B. ANDERSON.

POINTS FROM LETTERS

Aspirin Plain and Buffered

Mr. J. H. CHAPMAN (Chairman, Reckitt and Sons, Ltd., Hull) writes: Mr. W. Trillwood (*Journal*, February 28, p. 588) is quite right in saying that the aspirin in an ordinary 5 gr. (0.324 g.) aspirin tablet will, given sufficient time, dissolve in 100 ml. of water at 20° C. (68° F.), but the important point is that this takes place only slowly, whereas with soluble aspirin, as in "solprin," solution of the aspirin is rapid. My reference to controlled conditions was not, of course, intended to suggest that patients take aspirin under such conditions, but that controlled conditions are essential for valid comparative tests of solubility to be made. Under such conditions, as previously stated, it can readily be shown that the aspirin in solprin passes rapidly into solution, whereas the aspirin in ordinary aspirin 5-gr. tablets, even of the readily disintegrating type, does not.

Hypodermic Needles

Dr. E. B. PHILLIPS (Bridgend, Glamorgan) writes: May I pass on a tip which should save hospitals and practitioners many thousands of needles and pounds each year in the matter of blocked needles? When these have been blocked by penicillin, the affected needle should be affixed to a syringe filled with water. The needle is then passed through a gas jet so that the tip is heated with gentle pressure applied to the syringe. In a second or two the needle is free and a jet of water will issue. Blunt needles can easily be sharpened with very fine carborundum paper, if the angle of the tip is observed and followed in the four directions. . . . If the needle is first taken lightly over the thumb nail, it can soon be seen whether it is blunt or not, with the saving of much consequent pain to the apprehensive patient.

Obituary

P. E. BARBER, Ch.M., M.R.C.S., L.R.C.P.

Professor P. E. Barber, formerly professor of midwifery in the University of Sheffield, died at his home at Ashford, near Bakewell, Derbyshire, on April 24. He was 96 years of age.

Percival Ellison Barber was born on July 20, 1862. He came of a well-known Sheffield family that has had several generations of medical members. His father, Mr. Jonathan Barber, was senior surgeon at Sheffield Royal Infirmary and honorary secretary of the medical school, in which for many years he was the lecturer in surgery and forensic medicine. From Caius College, Cambridge, Percival Barber went on to St. Bartholomew's Hospital to receive his clinical training, and qualified M.R.C.S., L.R.C.P. in 1886. In that year he was appointed assistant house-surgeon at Sheffield Royal Hospital, later becoming house-surgeon. In those days there was a visiting dispensary in connexion with the hospital and each house-surgeon had to visit patients each day at their homes. Early on in his career he decided to specialize in obstetrics and gynaecology, and so became a house-surgeon at the Jessop Hospital for Women, Sheffield. Later, after he had entered general practice in Sheffield, he became an honorary surgeon on the staff of that hospital. He was also demonstrator in anatomy at University College, Sheffield, and later became lecturer and instructor in vaccination at the college.

Barber played an important part in the formation and development of the medical faculty in the University of Sheffield, which was established in 1905. In 1911 he was appointed professor of midwifery in the university and occupied the chair until he retired in 1921. He was granted the degree of Ch.M. (*ex officio*) by the university in 1920. When the British Medical Association held its Annual Meeting at Sheffield in 1908 he acted as one of the honorary secretaries of the Section of Obstetrics and Gynaecology. A keen member of the old Volunteer Force—he was a surgeon-captain attached to the 4th West Yorkshire artillery—he continued to show the same interest as an officer in the Territorial Army. During the first world war he served in home hospitals as a major in the R.A.M.C., and in 1929 was awarded the Territorial Decoration. As assistant county director of the Red Cross in Derbyshire, he delivered lectures in many parts of the county during the second world war. In his younger days he was a useful all-rounder at cricket, and played for his college, his hospital, and the United Hospitals. Almost to the end of his long life he displayed the vigour, both physically and mentally, of a much younger man, and he was always delighted to talk about his early days in Sheffield. He leaves a widow, a son, and a daughter, to whom we extend our sympathy.

C. de B. THOMSON, L.M.S.S.A.

Dr. C. de B. Thomson, for many years senior anaesthetist to Willesden General Hospital, died suddenly on April 5. He was 69 years of age.

Claude de Boudry Thomson was born in Melbourne, Australia, on April 22, 1889, and was brought to England by his father, who took up the practice of dental surgery in Torquay, and later in Harley Street. He went to Epsom College and later returned to Australia, intending to train for holy orders. A slight but unpredictable impediment of speech made him feel that his *métier* lay elsewhere, and he returned to England in 1913, qualifying L.M.S.S.A. from the Middlesex Hospital in 1919. He went to Willesden soon afterwards, and took up general practice in Queen's Park. He had early developed an interest in anaesthetics, and soon established a reputation in this field, so that when a vacancy occurred in 1925 in the Willesden General Hospital, then just emerging from a cottage to a first-rate, if small, general hospital, de Boudry Thomson was appointed, and there began an association which was to last 33 years.

M. M. writes: With the untimely death of Claude de Boudry Thomson, so soon after that of his friend and colleague, Pearse Williams, the Willesden General Hospital and the Willesden Division of the B.M.A. have to mourn the loss of a notable figure, for de Boudry Thomson was a by-word in Willesden for over 30 years as an outstanding general practitioner and anaesthetist. He entered with characteristic vigour and enthusiasm into local medical affairs in all their aspects, served for many years on the executive committee of the Willesden Division of the British Medical Association, and filled the office of chairman of the Division with great distinction in 1934–5. He was also a member of the old London Insurance Committee, and more recently of the Middlesex Local Medical Committee. His interests in the medical field were many, and among his numerous honorary appointments was that of honorary medical officer to the Adoption Society. He was something of a *bon viveur*, and showed considerable expertness in his views on good food and wine. Those of us who were present will not soon forget the delightful and intimate presidential dinner arranged by him, in honour of Pearse Williams, first president of the Willesden General Hospital Medical Society. He was also a keen photographer, and when he retired from the hospital in July, 1958, his colleagues presented him with a fine camera, which he was observed to be using to great effect on the recent occasion of the presidential address given by Mr. F. W. M. Pratt to the Medical Society. But perhaps his greatest enthusiasm was for caravanning, and it was in fact in his caravan that his sudden and fatal illness overtook him. His fine and distinguished presence would have graced any walk of life, and the Church's loss was Medicine's gain. He will be greatly missed by a host of patients, colleagues, and friends.

D. GLANVILLE EVANS, M.B., B.Ch.

Dr. D. Glanville Evans, who was in general practice in Pwllheli, Caernarvonshire, for many years, died at his home there on April 2. He was 51 years of age.

David Glanville Evans was born on April 20, 1907, and was educated at Cardiff High School, the School of Medicine, Cardiff, and University College Hospital, London. He graduated M.B., B.Ch. (Wales) and M.B., B.S. (London) in 1930. After holding the posts of casualty officer at the National Temperance Hospital, London, and house-physician at Cardiff Royal Infirmary, he became an assistant to Dr. John Griffydd, Bethesda, and after two years joined Dr. Idris Jones, an old college friend, in practice in Pwllheli. He served in the R.A.F.V.R. throughout the second world war, first in France and then for three years at the R.A.F. Hospital, Aden, and was mentioned in dispatches in 1943. On returning to Britain he went first to the R.A.F. Hospital, Cosford, and from there to the R.A.F. Hospital, Wroughton.

When he was discharged from the R.A.F. he returned to Pwllheli and took an active part in everything concerning the district, to which he was deeply attached. He was a member of the local medical committee, a medical officer at Bryn Beryl Hospital, vice-chairman of the benevolent branch of the British Legion, and a member of the town council. He was also the vicar's warden and a member of the governing body of the Church in Wales. He had a warm humanity and his patients thought of him always as their friend as well as their doctor. A very large number of people, both young and old, feel a sense of deep loss in his death.

J. G. J. writes: I first knew Glanville Evans during his student days at U.C.H. When, many years later, our acquaintance was renewed on his return to Pwllheli from war service, it was with pride that I recalled our former

association, for here was a general practitioner whose work and skill were in keeping with the highest traditions of our medical school. He was an indefatigable worker, travelling scores of miles daily over his extensive practice. A fast but very reliable driver, he was a familiar figure on the lanes of Lleyn, and his patients knew that an urgent call would be answered as promptly as it was made. In addition, he participated freely in religious, municipal, and social activities, and no doubt this contributed to his very wide store of human understanding. This faculty was of particular assistance to any consultant whom he might summon, because the latter is entirely dependent on the general practitioner for the psychological background to a case, and Glanville was as particular about such details as of the results of his careful clinical examination. Further, his influence in persuading his patients to accept the consultant's advice was invaluable among a local community still somewhat fatalistic in its attitude to disease. Glanville's career ended all too soon. When he recovered partially from his first serious illness he knew that it could not be for long, but he got back to work, being determined to die in harness. This he achieved, and his friends are glad of it, because he loved life, he loved work, and above all he loved people. In return, his people loved and trusted him. The vast congregation that filled St. Peter's Church for the impressive funeral service was in itself proof of the esteem in which he was held. His medical colleagues, too, grieve for the loss of a loyal friend and join in the sympathy which is universally extended to his wife, Dr. Margaret Evans, and to their son and daughter.

M. J. EVANS, M.B., B.S., D.P.H.

Dr. M. J. Evans, who was in general practice at Llandybie, Carmarthenshire, for 25 years, died suddenly at his home there on April 12. He was 53 years of age.

Myrddin James Evans was born at Cardiff on August 9, 1905, the second son of Mr. Howell T. Evans, M.A., the Welsh historian and some time master at Cardiff High School and subsequently headmaster of Aberaeron County School. After receiving his earlier education at both schools, he entered the Cardiff medical school for his pre-clinical training and then went on to St. Bartholomew's Hospital. He took the London Conjoint diploma in 1928 and the London degrees of M.B., B.S. in the following year. In 1931 he obtained the D.P.H. of the English Royal Colleges. After qualification he held resident appointments at the Jenny Lind Hospital for Children, Norwich, Battersea General Hospital, and Aberystwyth Infirmary before taking assistantships at Redhill, Surrey, and Llanelly—work in which he was very happy.

He then took over a large single-handed practice in a rural area on the fringe of the anthracite coalfield at Llandybie exactly 25 years ago. He held an appointment at the Amman Valley Hospital, and was medical officer of health under the Llandilo rural district council. A very active member of the British Medical Association, he was a member of the executive committee of the South-West Wales Division and of the South Wales and Monmouthshire Branch council for many years. He was chairman of the Division in 1951–2; a representative at the Annual Representative Meeting and a member of the Welsh Committee from 1954 to 1958; and assistant secretary of the Carmarthenshire local medical committee for six years and secretary for five years. He was also a member of the Carmarthenshire executive council for the last 10 years. Just a month before he died he had been elected captain of the Llandilo golf club.

D. M. H. writes: Myrddin Evans's unexpected and untimely death came as a great shock, and all our thoughts immediately turned to his family. He had carried out his daily round till late on the Saturday afternoon, and shortly before midnight even did a late call. Truly he died in harness. Friendship, admiration, and respect for his memory brought a very large number of his colleagues, both general practitioners and consultants, and people from all walks of life, to his funeral. It was an impressive and moving tribute from a community of farmers and mine-workers and their wives to their family doctor who had served them constantly, skilfully, and well. Truly here was confirmation that they "thought the world of him" for his single-handed devoted care and friendship for 25 years.

Myrddin's early death proves the excessive strain that single-handed practice imposes upon one who seeks to serve all with unbounded enthusiasm and loyalty. Many medical men might possess more flamboyant qualities, displayed over a wider and more catholic field, but none possessed in more ample measure the things that matter—clinical ability and professional and moral integrity, which in this kind and gentle man were interchangeable. A man's value is in his essential goodness, and this must be displayed in everything he does. Myrddin gave always his maximum contribution. He possessed and enjoyed all the things that every family doctor values, the respect and regard of his patients, and the affection and admiration of his friends and colleagues, and he had a happy home. We shall miss him at the local medical committee and B.M.A. meetings and on the executive council. I shall miss a loyal and helpful colleague and a warm-hearted friend, and those of us who were privileged to enjoy the gracious hospitality of his home feel deeply the sense of personal loss. To his devoted brothers, Judge Meurig Evans, Mr. G. Rhys Evans, a consultant ear, nose, and throat surgeon at Sunderland, and Mr. Lyn Evans, Cardiff, we extend our condolence, and to his widow, daughter, and son (who is still at school) we extend our very deepest sympathy.

Medical Notes in Parliament

STATEMENT ON RADIATION HAZARDS

The PRIME MINISTER made his eagerly awaited statement on the reassessment of radiation dangers on April 28. It was a detailed exposition, circulated to M.P.s in written form, as its nature really demanded; but prefaced by a simple and short verbal summary given in advance to the House.

"I am advised," he said, "that, even if deposition of the strontium-90 that has already been injected into the stratosphere continues at the higher rate observed in the summer of 1958, the concentration of this substance in bone is unlikely to approach the level which the Medical Research Council advised in 1956 would require 'immediate consideration.'"

Full Text of Statement

The following is the text of the full statement:

The debris in the stratosphere resulting from test explosions of nuclear weapons contains radioactive materials, of which strontium-90 merits the most immediate attention. Their effect on the body has been discussed in authoritative reports, notably in the Medical Research Council's report entitled *The Hazards to Man of Nuclear and Allied Radiations* (Cmd. 9780, June, 1956) and in the report issued in August, 1958, by the United Nations Scientific Committee on the Effects of Atomic Radiation. The purpose of the present statement is to review the situation and to comment on inferences that have been made concerning the residence time of radioactive materials in the stratosphere.

Rate of Deposition of Fall-out

For several years, authorities in the United Kingdom and in many other countries have been making regular measurements of the rate of deposition of strontium-90 and other isotopes. Measurements since May, 1958, have indicated a general rise, involving an approximate doubling of the rate of deposition in rainfall in the United Kingdom.

The estimation of the fall-out likely to occur in the future depends, amongst other factors, on an assessment of the total amount of radioactivity in the "stratospheric reservoir." Such an assessment can be attempted in a number of ways, for example, by: (*a*) Direct measurement of the quantity of debris in the stratosphere. The United States Department of Defence has carried out an extensive series of investigations, using balloon-carried measuring equipment for this purpose; but the results

so far obtained are difficult to interpret and the method is not yet considered to be satisfactory. (*b*) Estimating the amount of fission products which have been injected into the stratosphere by nuclear explosions, and measuring the world-wide deposition which has already taken place. It is considered that knowledge of these factors is insufficiently precise to give reliable estimates. (*c*) Measuring the relative proportions of shorter and longer-lived fission products in fall-out at the time of deposition, so as to give a broad indication of the average length of time of residence of fission products in the stratosphere, and measuring the fission product fall-out rate. The estimate of the size of the reservoir obtained in this way is directly proportional to the assumed length of the residence time.

The Report of the United Nations Scientific Committee on the Effects of Atomic Radiation contains, in paragraph 97 of Annexe D, the following observations on this subject: "Analysis of fall-out material has shown that strontium-90 can remain in the stratosphere for many years before being deposited on the earth. The depletion mechanism of the stratospheric reservoir is not yet adequately known. It has been estimated from measurement of fall-out rate and stratospheric content that the annual strontium-90 fall-out is about 12% of the stratospheric content. This annual fraction corresponds to a mean residence time of about eight years, which is in agreement with a value of 10 ± five years derived from unpublished data. The concept of a constant fractional removal per year of the stratospheric content is inconsistent with meteorological principle. However, nothing better can be offered at present. If the concept is to be used, a mean residence time of about five years appears to be the best value and a reasonable upper limit is about 10 years. The latter value has been used in the calculations to follow, since it tends to yield results on the pessimistic side."

It has recently been suggested, notably by the U.S. Department of Defence, on the basis of an interpretation of their measurements, that the residence time of radioactive materials in the stratosphere has been over-estimated. If this were true, it would confirm that the estimates made by the United Nations Scientific Committee were unnecessarily pessimistic, since there would be less of this material at present in the stratosphere than they estimated. There is some evidence to suggest that debris may leave the stratosphere more quickly from explosions in high latitudes than from explosions nearer the Equator. A shorter residence time would mean that the radioactivity would have had less time to decay before the fall-out was deposited; but strontium-90 decays so slowly that the difference would be very small. There would also be an increased amount of shorter-lived fission products in the fall-out, but the increase in the dose to body tissues from these would also be relatively small.

Once radioactive materials have left the stratosphere and entered the troposphere the local rate of deposition depends very largely on rainfall. Heavy rain tends to produce enhanced fall-out. This is certainly one of the factors responsible for the higher recorded measurements of fall-out in the summer of 1958. However, in subsequent months in which the rainfall in the United Kingdom was more nearly normal, the data so far available indicate that the rate continued high. There is evidence from the nature of the radioactive material deposited that this is likely to have been due to recent tests, presumably those conducted in the autumn by the U.S.S.R., the fall-out from which possibly occurred more rapidly because they took place in high latitudes. The so-called "Argus" experiments conducted about the same time by the United States are understood to have been three low-yield nuclear explosions at great heights: they therefore resulted in only a very small addition to the radioactivity already in the stratosphere.

Monitoring of Strontium-90 in Diet

In this country, regular measurements are made of strontium-90 in food, milk, drinking-water, and air, and in soil and vegetation. We thus have much information on the rate at which strontium-90 enters the diet and reaches bone. The investigations of radioactivity in food were considerably expanded in 1958. Milk receives special attention because much of the total strontium-90 in diet comes from dairy produce. Representative samples are collected regularly from over 200 depots handling some 40% of the total milk production in the United Kingdom. So far as is known, no equally comprehensive scheme is in operation in any other country. Other foods which introduce considerably less strontium-90 into the diet are also examined; for example, cereals, both imported and home-produced, and vegetables.

The measurements of very low levels of strontium-90 involve lengthy and complex processes of analysis, using specialized techniques and facilities. The results of the food survey for 1958 are now being prepared for publication. They indicate that, although the extent of contamination varies between different parts of the country, the amounts of strontium-90 in food and drinking-water are well below those which are likely to give rise to concentrations in human bone, which, in the words of the M.R.C. report, would require "immediate consideration."

The quantity of strontium-90 in diet at the present time depends mainly on what has been deposited in the preceding few months, rather than on the total deposition since fall-out began. Most of the strontium-90 taken up by cattle is that freshly deposited on herbage before it has had a chance to be washed into the soil. The quantity of strontium-90 in human diet in the U.K. rose much less in 1958 than did the rate of deposition; this may have been largely due to heavy rain washing strontium-90 from herbage into the soil. Once strontium-90 has entered the soil it may still be absorbed through the roots of grass and other crops, but the amount at present taken up in this way is relatively small.

If the enhanced rate of fall-out which began in the middle of 1958 continues in 1959, an increase in the strontium-90 content of diet is to be expected. Because the contamination of food is dependent on the rate of deposition in the immediate past, no precise prediction of the future situation can be made; but the evidence now available leads to the view that the concentration in human bone of strontium-90 attributable to what has already been injected into the stratosphere is likely to remain below that at which immediate consideration would be necessary.

Strontium-90 in Human Bones

A recent U.K. report has given the results of further measurements of strontium-90 in samples of human (mainly children's) bones from the first few months of 1958. The measurements on bones of 59 children (stillborn or dying under the age of 5 from various causes) showed only a slight increase as compared with corresponding results for 1957. These results accord with what was to be expected, since the level of strontium-90 in the diet in the relevant period had increased very little as compared with the previous year.

The irradiation of human bone and bone marrow attributable to strontium-90 is at present small in relation to that from the natural radioactivity to which they are exposed; the variation in natural radiation levels from place to place in the U.K. (and elsewhere) is far greater than the additional radiation likely to arise from tests already conducted.

Other Radioactive Materials

Attention is given also to other radioactive materials, for example caesium-137, plutonium, and carbon-14. The extent of the effort devoted to the study of these substances is kept under regular review in the light of the changing fall-out situation.

Results of measurements of caesium-137 in water, milk, and the human body in the United Kingdom have been published. Caesium-137 is not readily taken up from the soil by plants, and, unlike strontium-90, is not retained in the body for long periods. Its biological significance arises from genetic effects, the magnitude of which depends on the gonad dose incurred. This has been discussed in the report of the United Nations Scientific Committee on the Effects of Atomic Radiation (Chapters III, VI, and VII). The dose to the gonads delivered by caesium-137 is small in relation to variations in natural radiation between different parts of this country.

The incorporation into the body of plutonium from fall-out is small in importance compared with that of strontium-90, since plutonium is only very slightly absorbed from food. Both materials can be absorbed through inhalation, but this is a minor source of intake.

For several years measurements have been made of the concentration of carbon-14 in air and in biological material. Carbon-14 occurs naturally from the effects of cosmic radiation, but some also comes from weapon tests. This subject has been under consideration by the United Nations Scientific Committee (Document A/AC.82/INF.3, July 23, 1958). The concentration of carbon-14 is being kept under review because of its long persistence, notwithstanding the very low rate of irradiation that it causes in the human body.

QUESTIONS IN THE COMMONS

Distribution of Polio Vaccine

Dr. EDITH SUMMERSKILL (Warrington, Lab.) was one of six M.P.s who questioned the Minister of Health on April 27 about, in her words, "the recent maldistribution of poliomyelitis vaccine."

Mr. D. WALKER-SMITH stated that vaccine was allocated on the basis of monthly requisitions from local health

authorities, whose estimated needs for this month were delivered by April 4. A very welcome though belated rise occurred, shortly after that date, in the response from young people, of whom only one in twelve had registered for vaccination by the end of February. As, however, it came very suddenly and was unexpectedly steep, a considerable number of local health authorities had to ask urgently for additional supplies of vaccine. These requests had all been met, a million extra doses having been distributed. Further large supplies would be issued to meet the needs of May, including a million doses of imported Salk and the vaccine available from British producers.

In reply to Mr. W. R. WILLIAMS (Manchester, Openshaw, Lab.) Mr. WALKER-SMITH insisted that there was no question of any wholesale breakdown, and it was quite wrong to suggest there was. What happened was that some local authorities, instead of requiring a preliminary registration, vaccinated on demand at open clinics, first to encourage young people to come forward and then to cope with the large numbers. In doing so on that basis there were necessarily occasional local difficulties of supply.

Alleged Threat to Third Injections

Dr. SUMMERSKILL told the Minister he was making a great mistake in adopting this attitude. The six questions represented the views of medical officers of health in different parts of the country. She produced some letters, and asserted that the Middlesex County Council in the previous week had told doctors that promises made to the council of supplies of vaccine had not been fulfilled, that no further vaccine would be available until May, that the only way the authority could meet its commitments was to refuse any third injection, and that people applying then could be given only one injection.

Mr. Walker-Smith's reply was that only one injection was given to start with, and a second after four or five weeks. He was certain—although speaking without notice—that the Middlesex demands, or supplementary demands, had been or were being met in the course of the week. Dr. SUMMERSKILL: The instructions were that children who were ready for their third injection, which would give them full protection this summer, were not to be given it, but that that injection was to be given to new cases. Mr. WALKER-SMITH stated that it was within the discretion of each local authority how it arranged its programme.

Cost of Polio Vaccine

The MINISTER told Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) that 26½ million doses of vaccine had been distributed, of which 10½ million had been British and 16 million imported.

Mr. S. P. VIANT (Willesden, West, Lab.), who asked about costs, was informed that the cost to the Exchequer of the vaccine for a series of three inoculations was estimated at between 10s. and 12s. The cost to local authorities of arranging for the vaccine to be administered varied according to the arrangements made, and an estimate was not available. No charge was made to the persons vaccinated.

Increase In Leprosy

The MINISTER informed Mr. Norman Pannell (Liverpool, Kirkdale, Con.) that at the end of 1958 there were 275 cases of leprosy known in the United Kingdom. Mr. PANNELL pointed out that the number had risen from 46 cases in 1951, and asked what was the reason for this alarming increase. Mr. WALKER-SMITH said that the disease was contracted outside this country, and for that reason he could not say to what the increase was due.

Mr. PANNELL thought the situation was becoming so serious that some regulations should be observed, particularly in regard to people entering the country suffering from the disease. Mr. WALKER-SMITH did not think it could be described as serious. There was no evidence of a spread of leprosy in this country. He also told him that there were two special units in England and Wales where in-patient treatment was given, one of which was outside the Health Service. In addition many sufferers from leprosy could be treated as out-patients at hospitals without special facilities. In Scotland patients were treated at any major infectious diseases hospital or at the tropical diseases unit of the Eastern General Hospital, Edinburgh.

Doctors' Pay

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) asked when the Minister expected to receive the report of the Royal Commission on doctors' pay. Mr. WALKER-SMITH: The Royal Commission expect to receive all outstanding information by the autumn and thereafter they will report as soon as possible.

Mr. ROBINSON: Was not the Royal Commission asked to make its report as a matter of urgency? The last information from the Minister was that he expected the report this summer. Why has there been further delay? Mr. WALKER-SMITH: The Royal Commission is proceeding as quickly as it can compatible with doing the job it was asked to do. I pass on expectations as I receive them from the Royal Commission.

Part-time Consultants

Mr. KENNETH ROBINSON, also asked, how many whole-time consultants had transferred to part-time maximum sessions in each of the last five years for which figures were available. Mr. WALKER-SMITH said that information was not immediately available. He was having the necessary inquiries made, and would write to Mr. Robinson as soon as possible.

Mr. ROBINSON said the information ought to be available to Parliament. These transfers from whole-time to part-time, however financially advantageous to consultants, were detrimental to the hospital service and should be discouraged, not only by the Ministry but also by the Inland Revenue. Mr. WALKER-SMITH replied that the information would be available when he had made inquiries. At the end of this year improved statistical procedures would enable such information to be given without making individual inquiries. Mr. Robinson would be aware of the safeguarding of part-time consultant work by section 12 of the National Health Service (Amendment) Act, 1949.

On the last part of his question, they had better wait and see whether the Royal Commission had anything to say when it reported.

Chiropody Service

Mr. WALKER-SMITH, replying to questions by Mr. J. McKay (Wallsend, Lab.) about the registration scheme for chiropodists taking part in the Health Service, said the difference arose between the point of view of the medical auxiliaries and the Joint Consultants' Committee. He had been seeking to help to resolve that difference. The Secretary of State for Scotland and he were now considering points put forward by the Joint Consultants' Committee.

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on January 22 the degree of B.M. was conferred on M. A. Rucklidge, L. M. McEwen, and, in absence, on J. Dodd.

UNIVERSITY OF CAMBRIDGE

In Congregation on January 24 the following degrees were conferred:

M.B., B.CHIR.—*N. A. Subedar, *R. W. Sherwin, G. D. Blackledge, *A. A. Wilkinson, *R. V. F. Williams, *L. Kwasny, *A. H. Y. Lee.

M.B.—*P. H. T. Greig, *W. T. Menke, *D. Rhys-Phillips, M. J. Raphael, *J. M. Ll. Jones, R. M. Simons, J. Blake, J. W. Soper, J. R. Strong, *D. B. MacAdam, T. Moreton.

*By proxy.

UNIVERSITY OF LONDON

In December, 1958, the degree of Ph.D. in the Faculty of Medicine was awarded to J. R. Nixon (Chelsea College of Science and Technology) and R. Hardman (University of Nottingham).

Medico-Legal

HOSPITAL SWILL

[FROM OUR LEGAL CORRESPONDENT]

At Woodplumpton 21 pigs died after eating swill collected from a hospital, alleged a pig-keeper at Preston County Court on March 10. The pig-keeper was awarded £331 10s. damages against the Preston and Chorley Hospital Management Committee, but he did not contest the Committee's claim against him for £98 8s. for breach of contract (*The Times*, March 11). The Committee's explanation of the fatalities was that sometimes the swill accumulated uncollected for three days and as a result had to be put into bins normally reserved for other hospital waste such as dressings and ashes.

If the pig-keeper was in breach of a duty, contractual or otherwise, to remove the swill more often than once every three days, that would not totally absolve the management committee from their duty to him in negligence. But the pig-keeper's duty might be relevant, as contributory negligence, in the reduction of damages.

Hospital authorities are generally mindful of the duty of care imposed on them by the law of negligence in respect of patients, visitors, and employees entering the hospital by the front door: but it is easy for them to forget the pig-keeper who comes to the back door. In a classic statement of the law[1] Lord Atkin said that everyone owes a duty of care to his neighbour. "The rule that you are to love your neighbour becomes, in law, you must not injure your neighbour;"—i.e., injure him in his property as well as his person—"and the lawyer's question, Who is my neighbour? receives a restricted reply. You must take reasonable care to avoid acts or omissions which you can reasonably foresee would be likely to injure your neighbour. Who, then, in law is my neighbour? The answer seems to be—persons who are so closely and directly affected by my act that I ought reasonably to have them in contemplation as being so affected when I am directing my mind to the acts or omission which are called in question." Thus the pig-keeper collecting the swill is as much a neighbour of the hospital authority as the patient on the operating table, though the standard of care owed to him is not so great as that owed to patients.

Vital Statistics

Industrial Accidents and Diseases

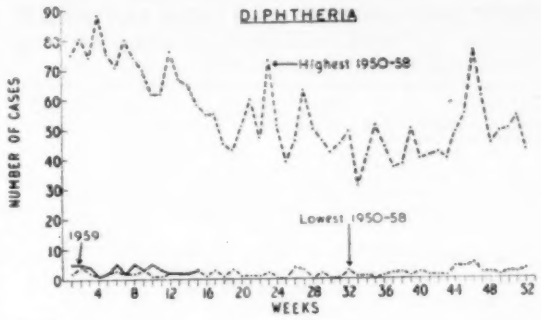
The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in March was 112, compared with 108 in the previous month and 121 in March, 1958.

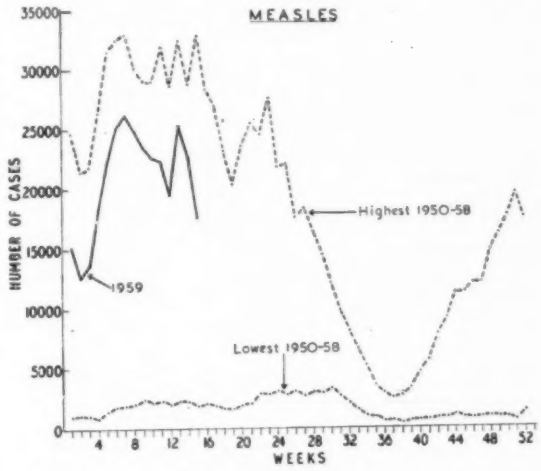
The numbers of cases of industrial diseases in the United Kingdom reported during March, 1959, were as follows: Lead poisoning 2, compressed air illness 1, epitheliomatous ulceration 7, chrome ulceration 10; total 20. There were 2 deaths from epitheliomatous ulceration due to mineral oil.—*Ministry of Labour Gazette*, April, 1959.

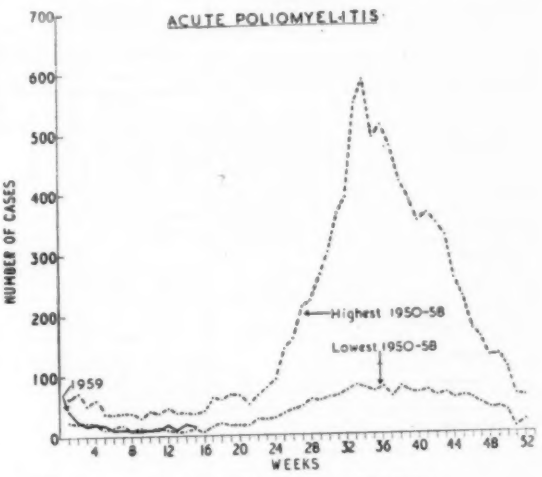
Graphs of Infectious Diseases

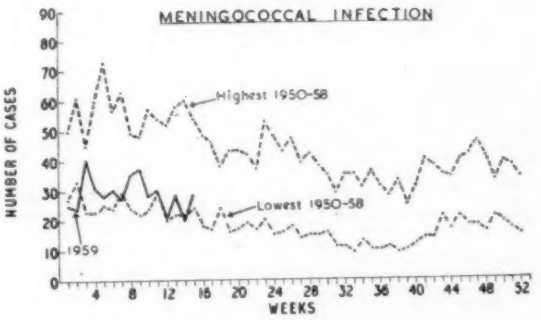
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.

[1] *Donoghue* v. *Stevenson* [1932] A.C. 562.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 18** (No. 15) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria ..	3	0	5	0	1	4	0	1	0	
Dysentery ..	806	115	148	27		863	71	203	7	6
Encephalitis, acute	4	0		0		3	1		0	
Enteric fever:										
Typhoid ..	0	0	1	0		3	1	0	0	
Paratyphoid ..	6	3	1(B)	0		2	1	1(B)	0	4(B)
Food-poisoning ..	160	48	10	0		112	11	13	1	
Infective enteritis or diarrhoea under 2 years				7	16				12	18
Measles*	17,696	972	1674	443	296	5,066	281	131	37	8
Meningococcal infection	29	6	17	0	1	24	2	16	0	7
Ophthalmia neonatorum	28	1	8	0		23	1	2	0	
Pneumonia† ..	510	25	254	9	14	585	44	323	4	3
Poliomyelitis, acute:										
Paralytic ..	12	1	0	0	1	9	0	2	0	4
Non-paralytic ..	3	0	0			2	0			
Puerperal fever‡ ..	200	27	14	1		244	36	17	1	1
Scarlet fever ..	671	23	63	25	23	738	53	56	24	28
Tuberculosis:										
Respiratory ..	661	60	99	26		458	59	148	14	
Non-respiratory	66	2	12	0		73	5	16	2	
Whooping-cough	623	24	88	33	94	495	33	31	6	4

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria ..	0	0	0	0	0	1	0	0	0	0
Dysentery ..	0	0		0		2	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	2	0	1	7	0	2	0	1
Influenza	116	2	2	4	9	57	1	1	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		1	0				1	0		
Pneumonia ..	640	49	18	13		719	63	42	18	8
Poliomyelitis, acute	0	0		0	0	1	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	81	3	8	0	3	96	5	12	2	6
Non-respiratory		0	1	0	1		0	6	0	0
Whooping-cough	1	0	0	1	0	1	0	0	0	1
Deaths 0–1 year ..	314	38	42	9	24	336	36	46	8	12
Deaths (excluding stillbirths) ..	10,307	791	583	147	247	11,280	933	783	137	194
LIVE BIRTHS ..	14,600	1219	1016	275	454	14,710	1319	1149	239	420
STILLBIRTHS ..	347	21	34			378	27	34		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
‡ Includes puerperal pyrexia.

Medical News

Differential Salary Scales in South Africa.—The South African Medical and Dental Council has questioned the Government's policy of paying non-white medical practitioners less than white doctors when they are doing the same work under the same employing authority. The subject of differential salary scales was debated at the Council's half-yearly meeting in March, and a motion was carried that the Council's president and vice-president should discuss the implications of this differentiation with the Minister of Health. During the debate, Professor I. GORDON, dean of the faculty of medicine at Natal University, suggested that a non-European practitioner who accepted a post under these conditions might be offending against the Council's ethical rules in that the remuneration was "derogatory to the medical profession," "inimical to the interests of the public," and in that he was "permitting himself to be exploited in a manner detrimental to the public or professional interest." He believed that non-European graduates would turn their eyes to African territories in the North, and thus the Government's own policy of providing medical services for the native community in South Africa was in danger of being defeated.

"Wellcome Trust's Second Report, 1956–8."—The trustees allocated roughly as great a sum for research in the two years covered by this report as was made available in the previous 20 years—a sum in the region of £1m. The earlier period was rendered in many respects a highly abnormal one by the complexities of establishing the Trust, dealing with the heavy estate duties, and by difficulties during and after the war. The present report, accordingly, is the first which the trustees have been able to present for a period which they can regard as wholly normal from the administrative point of view. In general, the policy of the Trust and the pattern of its benefactions remain the same, but, in keeping with the world-wide organization of the Wellcome Foundation Limited, from which they derive their income, the trustees have increased the magnitude and range of their support for research in countries overseas. Their scheme, an innovation of its kind, for providing Wellcome Research Travel Grants for those who are actively engaged in research has steadily increased in scope since it was first introduced in September, 1955.

Oestrogens in Farming.—The Agricultural Research Council has not yet completed its inquiry into the possible dangers, whether to man or animals, of administering synthetic oestrogens to stock and poultry in order to fatten them. However, in the meantime, farmers are warned against the implantation or feeding of breeding stock with stilboestrol or hexoestrol, and, further, that the overdosing of animals intended for slaughter may "possibly render the meat less attractive, although not dangerous to the consumer." Since swallowing or even inhaling small amounts of these substances can have serious toxic effects on man, attention is drawn to the dangers of home-mixing them on the farm with other feeding stuffs. It is emphasized that all oestrogen-containing substances should be kept in a safe place, and, in particular, well away from children. These points were made in a joint announcement by the Agricultural Departments of Great Britain on April 28.

Association of the British Pharmaceutical Industry.—Dr. THOMAS KERFOOT presided at the annual dinner held in London last week. Speaking of the importance of research to the pharmaceutical industry, he said that if the quantity of research done in Britain was small by certain standards the quality was superb. He thought that the political and social value of drugs introduced by the pharmaceutical industry for the cure of tropical diseases had been underestimated. More should be done to publicize the achievements of the industry. Dr. Kerfoot said they were aware of the importance of keeping their own house in order, and a marketing code for medical specialties had been drawn

up and accepted by every member of the association. Speaking in reply, Mr. DEREK WALKER-SMITH, Minister of Health, emphasized the importance of the contributions made by the pharmaceutical industry to export trade. "Every citizen in this country," he said, "shares an interest in overseas trade. Exports are the prop and stay of our economy." On the subject of the price of drugs in the N.H.S., Mr. Walker-Smith said that it was not easy to devise a satisfactory formula for pricing. Consideration was being given to "weighting" in relation to research on the one hand and large-scale production on the other. Welcoming the public's new zeal for vaccination, Mr. Walker-Smith quoted the latest figures for the distribution of poliomyelitis vaccine: in all, over 26 million doses had been distributed, 5½ million of them in the last month or so.

British Association of Physical Medicine.—The sixteenth annual meeting of the British Association of Physical Medicine was held at Guy's Hospital last month. The retiring president, Dr. P. BAUWENS, was in the chair. The scientific programme included a symposium on "Graphical Representation of Movement," a discussion on "The Spine," and a number of short papers read by members of the association and by guest speakers. Among the subjects of these papers were accidents in departments of physical medicine and rehabilitation, intra-articular prednisolone therapy, antimalarial drugs in the treatment of rheumatoid arthritis, electromyography of the anal sphincter in health and disease, and the treatment of tennis elbow. At the annual general meeting of the association the following officers were elected: president, Dr. H. A. Burt; vice-president, Dr. W. S. Tegner; honorary treasurer, Dr. J. Shulman; honorary secretary, Dr. A. T. Richardson; and honorary editor, Dr. A. C. Boyle. The annual dinner of the association was held at the Stationers' Hall.

University Apartheid.—The South African House of Assembly passed the last stage of the Separate University Education Bill on April 30. The Bill now has to go through the Senate before becoming law.

Mr. A. H. Barber, who applied for a post as consultant obstetrician and gynaecologist with the South Manchester group of hospitals, has not been selected. A recommendation appointing another candidate was made at a meeting of the Board's advisory appointments committee on April 28. The post is the first of its kind to be advertised in the region since the Manchester Regional Hospital Board was told by the Minister of Health that it had "a moral obligation" to assist Mr. Barber (*Journal*, March 14, p. 702).

Mr. V. B. Green-Armytage has been elected an honorary fellow of the Obstetrical and Gynaecological Society of Portugal.

Mr. Charles Macmillan, chairman and managing director of E. and S. Livingstone, Ltd., medical publishers, Edinburgh, has been appointed chairman of the Edinburgh, Mid- and East Lothian Disablement Advisory Committees. He succeeds the late Sir George Henderson.

COMING EVENTS

IV Festival International du Film Medico-Chirurgical d'Enseignement, de Prévention et d'Education Sanitaires.—This Festival will not take place in May as previously arranged but from September 11 to 14.

Faculty of Dental Surgery, R.C.S. (Eng.).—The department of dental science will be formally opened on May 22 by Lord COHEN OF BIRKENHEAD, who will also deliver the Charles Tomes Lecture on "Facial Neuralgias."

Faculty of Medicine, University of Paris.—A course on allergic disorders will be held from May 25 to 30 at the Clinique Médicale Propédeutique de l'Hôpital Broussais. Further details from the hospital, 96, rue Didot, Paris, 14.

Society for the Study of Infectious Disease.—Meeting to be held on May 30 at Ruchill Hospital. Details from Dr. J. B. LANDSMAN, Brownlee Laboratory, Ruchill Hospital, Glasgow, N.W.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, May 9

SCOTTISH OTOLARYNGOLOGICAL SOCIETY.—At Royal Infirmary, Edinburgh, 2 p.m., 78th meeting.

Monday, May 11

BRITISH ASSOCIATION OF SPORT AND MEDICINE.—At Meyerstein Lecture Theatre, Westminster Hospital Medical School, 5 p.m., Sir Adolphe Abrahams: Nutrition and Athletics.

PLYMOUTH MEDICAL SOCIETY.—At Greenbank, 8.30 p.m., annual general meeting.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. C. Popjak: Lipid Metabolism and Atheroma.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute of Microbiology, 5 p.m., Almroth Wright Lecture by Professor G. W. Beadle (California): Molecular Basis of Heredity.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, London, W.C., 5 p.m., public lecture by Dr. J. B. Neilands (U.S.A.): Iron Metabolism in Micro-organisms.

Tuesday, May 12

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., Professor Martin Roth: A New Neurotic Syndrome and its Bearing Upon the Classification of Neurotic Illness.

●GUY'S HOSPITAL MEDICAL SCHOOL.—At Physiology Lecture Theatre, 5 p.m., Fison Memorial Lecture by Sir George Thomson: Principles of Physics.

HEATHERWOOD ORTHOPAEDIC HOSPITAL.—8.30 p.m., Mr. E. W. Somerville: Congenital Dislocation of Hip.

INSTITUTE OF DERMATOLOGY.—At British Institute of Radiology, 5 p.m., Dr. G. E. Flatman: Radiotherapy of Benign Skin Conditions.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 2 p.m., Professor H. Carey (New Zealand): Staphylococcal Cross-infection in a Maternity Unit.

LONDON UNIVERSITY.—At Middlesex Hospital Medical School, Mortimer Street, W., 5.30 p.m. special university lecture in Medicine by Professor J. C. Beck (Montreal): Regulation of Adrenal Cortical Function.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Dr. Magnus Haines: Gynaecological Pathology.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. G. Parsons-Smith: Neurology.

Wednesday, May 13

INSTITUTE OF CHILD HEALTH.—5 p.m., Dr. David Yi-Yung Hsia (Chicago): Infant of the Diabetic Mother.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. Tickner: Biochemistry of Psoriasis.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. R. W. Riddell: Aspergilli as a Cause of Pulmonary Disorders.

OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Dr. Eliot Slater: Genetics of Mental Disease.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. E. F. Gale: Disorganization of the Bacterial Cell by Antibiotics.

Thursday, May 14

DENTAL IMPLANT SOCIETY OF GREAT BRITAIN.—At Royal Society of Medicine, 7.30 for 8 p.m., Professor Talmage Read will present his new film on Dental Implants.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 2.30 p.m., Professor G. Lennon: Induction of Labour.

LONDON UNIVERSITY.—At St. Thomas's Hospital Medical School, 5.30 p.m., special university lecture in human anatomy and morphology by Professor B. E. Ingelmark (Gothenburg): Functional Anatomy of the Locomotive Organs, Including the Spine.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. J. D. N. Nabarro: Chemotherapy of the Reticuloses.

ST GEORGE'S HOSPITAL MEDICAL SCHOOL.—5.30 p.m., Thomas Young Lecture by Professor P. B. Medawar, F.R.S.: Immunological Tolerance.

Friday, May 15

BRITISH COUNCIL FOR REHABILITATION.—At H.Q.S. "Wellington," Temple Stairs, Victoria Embankment, London, W.C., 3 p.m., annual general meeting. Dame Georgiana Buller Memorial Lecture by Dr. L. Guttman: Place of our Spiral Paraplegic Fellow-men in Society.

INSTITUTE OF DERMATOLOGY.—4.30 p.m., Dr. W. Frain-Bell: Primary Skin Cancer.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. G. B. Mitchell-Heggs.

LEICESTER CHRISTIAN MEDICAL ASSOCIATION.—At Leicester Royal Infirmary, 8.45 p.m., Mr. Cedric Harvey: Understanding the Child.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Dr. T. G. Ward: Management of Maxillo-facial Injuries.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Chamberlain.—On April 17, 1959, at St. George's Hospital, London, S.W., to Jocelyn (formerly Kerley), wife of Geoffrey Chamberlain, a son—Mark Peter.

Kenyon.—On April 4, 1959, at Queen Charlotte's Hospital, London, W., to Nuala and Islay Kenyon, a daughter—Nuala Rose Catriona.

Melville.—On April 24, 1959, at the Women's Hospital, Wolverhampton, Staffs, to Elizabeth Doreen (formerly Williams), M.B., B.Ch., and Herbert A. H. Melville, M.B., B.Ch., D.Obst.R.C.O.G., a son—David Harcourt.

Smith.—On April 23, 1959, at West Hill Hospital, Dartford, Kent, to Pat Allington Smith (formerly Frisby), M.B., B.S., wife of the Reverend R. A. Smith, a brother for Jeremy—Patrick.

DEATHS

Butler.—On April 7, 1959, at his home, 51, Grove Avenue, London, N., Frank Butler, M.R.C.S., L.R.C.P., L.D.S.

Shepheard-Walwyn.—On April 6, 1959, at Arllonby, Carlisle, Cumberland, Alfred Irving Shepheard-Walwyn, M.D., F.R.C.P.Ed., aged 77.

Thomson.—On April 5, 1959, Claude de Boudry Thomson, L.M.S.S.A., of 44a, Windermere Avenue, London, N.W.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Chemotherapy in Surgical Tuberculosis

Q.—*What is a suitable scheme of chemotherapy in the treatment of bone and joint tuberculosis? What are your views on the use of preparations such as "dipasic" (isoniazid aminosalicylate) over a prolonged period?*

A.—The principles of chemotherapy for the treatment of bone and joint tuberculosis are very similar to those for the treatment of lung tuberculosis. It should be remembered, however, that in some parts of this country bone and joint tuberculosis may still be due to the bovine tubercle bacillus and that a proportion of strains of bovine bacilli are naturally resistant to P.A.S. (para-aminosalicylic acid).[1] In general, the policy should be to use the combinations of drugs of proved efficacy in preventing drug resistance and to continue chemotherapy for a prolonged period, never less than one year and in most bone and joint conditions two years. In case the patient may have been infected with an organism primarily resistant to one of the standard drugs, it is wise to begin treatment with all three, streptomycin 1 g. daily by intramuscular injection, sodium P.A.S. 5 g. three times daily, and isoniazid 100 mg. twice a day. If it has not proved possible to culture tubercle bacilli initially and to test their drug sensitivity, then it is reasonable after three months to drop one of the drugs. In the case of adults one would usually stop P.A.S. and continue with the streptomycin and isoniazid. In the case of children one is more inclined to avoid injections and to stop the streptomycin. If a patient is over 40 daily streptomycin may give rise to giddiness. In such patients it is adequate to give the streptomycin injection three times a week in a dose of 1 g. After discharge from hospital it is most convenient to treat the patient with sodium P.A.S. 5 g. and isoniazid 100 mg., both given twice daily. Commercial preparations are available in which both drugs are combined in a single cachet. Four cachets twice a day give the appropriate dose. For children the daily dose of the drugs should be streptomycin 30 mg./kilo, P.A.S. 300 mg./kilo, and isoniazid 3 mg./kilo. The doses are divided as above.

The clinician should be very cautious in trying preparations said to be equivalent or superior to the standard three drugs. There is a great deal of evidence that dipasic, though it contains a small amount of P.A.S., in clinical practice is equivalent to isoniazid alone.[2–4] Clinically it is ineffective in the presence of isoniazid-resistant tubercle bacilli, and its use alone is liable to result in the patient's organisms becoming isoniazid-resistant. There are a number of other preparations which have been recommended as substitutes for P.A.S. which are said to be much better tolerated. Some of these have in fact little therapeutic effect, and, when employed with other drugs, may fail to prevent drug resistance.

REFERENCES

1 Wallace, A. T., and Webber, W. J., *Tubercle (Lond.)*, 1956, **37**, 358.
2 Walker, W. C., Hay, D., Stewart, Sheila M., and Crofton, J. W., ibid., 1957, **38**, 238.
3 Dunbar, J. M., and Ritchie, R. T., *Lancet*, 1957, **2**, 612.
4 Allan, G. W., McNaught, W., and Lees, A. W., ibid., 1957, **2**, 609.

Hazards of Fibreglass Manufacture

Q.—*What are the hazards of fibreglass manufacture, in which minute glass particles float in the air? Should masks be worn?*

A.—The properties of glass fibre and mineral wool are described by Fairhall.[1] He quotes experimental evidence and the results of radiographic examination of workers in the mineral wool industry which indicate that the dust is not harmful. Schepers *et al.*,[2] on the basis of animal experiments, also concluded that fibreglass-plastic dust produced lesions characteristic of the response to "inert" dusts. The observations suggested that the dust might cause exacerbation of tuberculous infection, and periodic *x*-ray examination of persons at risk was therefore recommended. Skin irritation is a common complaint among workers handling fibreglass. This is due to a mechanical effect: sensitization does not occur. Adequate exhaust ventilation to remove air-borne particles should be arranged and would be more effective than the wearing of masks in eliminating potential hazard.

REFERENCES

1 Fairhall, L. T., *Industrial Toxicology*, 1957, 2nd ed., p. 52. Williams and Wilkins Co., Baltimore.
2 Schepers, G. W. H., *et al.*, *A.M.A. Arch. industr. Hlth*, 1958, **18**, 34.

Male Fertility Tablets

Q.—*A patient says there has been an article in a magazine which states that there are some new tablets for increasing male fertility. Can you tell me what these tablets are?*

A.—New tablets for increasing male fertility receive publicity from time to time, but, so far as I am aware, none of them can be relied upon to achieve what is claimed for them. The tablets referred to could, for example, be arginine, for which claims were put forward some years ago in respect of their ability to promote male fertility, and which has recently been reinvestigated in Italy. It is doubtful if the claims were justified.

Polio Immunization and Dermatitis

Q.—*A patient who has intermittent dermatitis, diagnosed as neurodermatitis, wishes to be immunized against poliomyelitis. She has been warned that administration of a serum or vaccine might flare up the dermatitis. What would you advise?*

A.—It is true that vaccination against smallpox is apt seriously to aggravate a constitutional eczema and may occasionally give rise to Kaposi's varicelliform dermatitis, which is a serious complication. There is no such risk from vaccination against poliomyelitis, though there might be a transient aggravation with any constitutional disturbances which resulted. The poliomyelitis virus has no dermatological affinities. If immunization is deemed advisable I would not regard neurodermatitis as a sufficiently serious contraindication.

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